CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040011

Trade Name : METHAZOLAMIDE TABLETS USP

Generic Name: Methazolamide Tablets USP 25mg and 50mg

Sponsor : Applied Analytical Industries, Inc.

Approval Date: July 17, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040011

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Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040011

APPROVAL LETTER

ANDA 40-011

JUL 17 1997

Applied Analytical Industries, Inc.
Attention: Suzanne Yu
1206 N. 23rd Street
Wilmington, NC 28405

Dear Ms. Yu:

This is in reference to your abbreviated new drug application dated April 18, 1991, submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act, for Methazolamide Tablets USP, 25 mg and 50 mg.

Reference is also made to your amendments dated February 18 and November 23, 1992, July 18, 1995, October 17, 1996, and January 8, March 24, April 10, April 15, May 8, May 12, June 19 and June 23, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Methazolamide Tablets USP, 25 mg and 50 mg to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (Neptazane® Tablets, 25 mg and 50 mg, respectively, of Storz Ophthalmics Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

[redacted] 7-17-97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 40-011
Division File
Field Copy
HFD-600/Reading File
HFD-92
HFD-210/B.Poole
HFD-610/J.Phillips

Endorsements:

HFD-627/L.Huang [redacted] 4/28/97
HFD-627/P.Schwar[redacted] 4/28/97
HFD-613/L.Golson[redacted] 4/28/97
HFD-613/J.Grace [redacted] 4/29/97
HFD-617/J.Buccine/4/23/97 gp 4/30/97 7/10/97
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F/T by: gp/4/28/97
APPROVAL LETTER

[redacted] 7/14/97

[redacted]

7/16/97

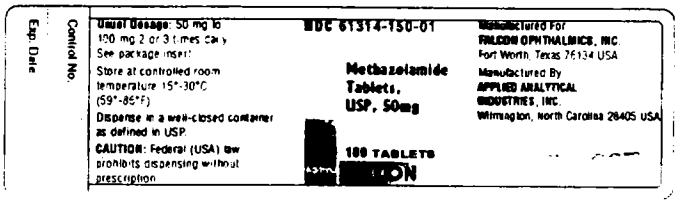
CENTER FOR DRUG EVALUATION AND RESEARCH

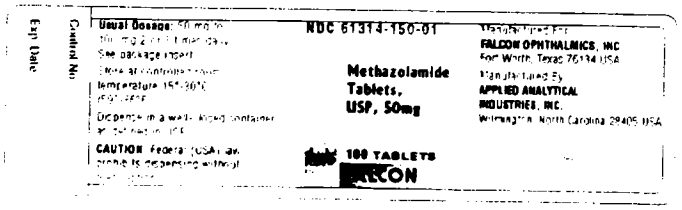
APPLICATION NUMBER 040011

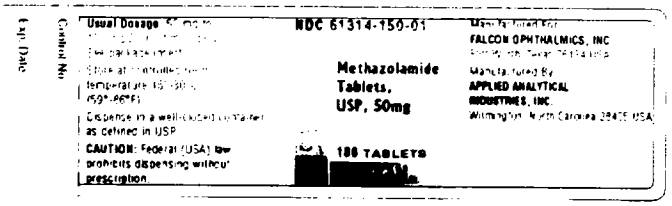
FINAL PRINTED LABELING

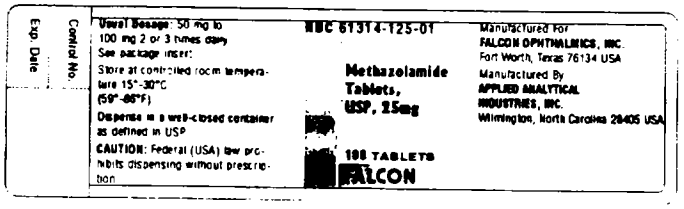
MAR 10

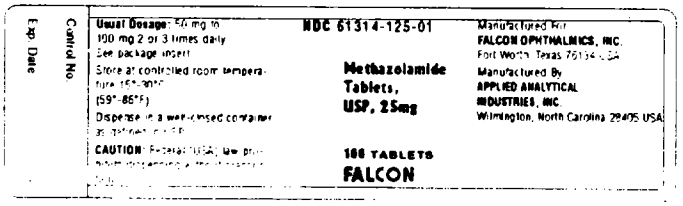
ANDA No. 40-011
Methazolamide Tablets, USP
25 mg and 50 mg








Exp. Date
Control No.
Usual Dosage: 50 mg to 100 mg 2 or 3 times daily
See package insert.
Store at controlled room temperature 15°-30°C (59°-86°F)
Dispense in a well-closed container as defined in USP
CAUTION: Federal (USA) law prohibits dispensing without prescription
NDC 61314-125-01
Methazolamide Tablets, USP, 25mg
100 TABLETS
FALCON
Manufactured For
FALCON OPHTHALMICS, INC.
Fort Worth, Texas 76134 USA
Manufactured By
APPLIED ANALYTICAL INDUSTRIES, INC.
Wilmington, North Carolina 28405 USA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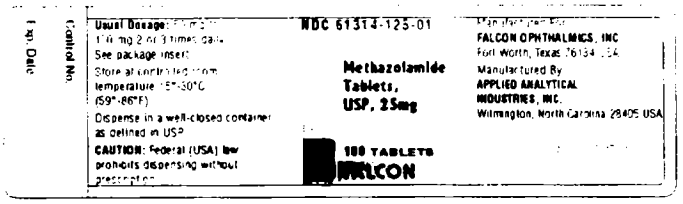
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100 TABLETS
FALCON
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Fort Worth, Texas 76134 USA
Manufactured By
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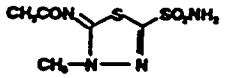
Wilmington, North Carolina 28405 USA

Methazolamide Tablets, USP

DESCRIPTION: Methazolamide, a sulfonamide derivative, is a white crystalline powder, weakly acidic, slightly soluble in water, alcohol and acetone. The chemical name for methazolamide is: N-[5-(aminosulfonyl)-3-methyl-1,3,4-thiadiazol-2(3H)-ylidene]-acetamide and it has the following structural formula:



Molecular formula: $C_5H_6N_4O_3S_2$

Molecular weight: 236.26

Methazolamide Tablets, USP, for oral administration, contains 25 mg or 50 mg methazolamide. In addition, each tablet contains the following inactive ingredients: Microcrystalline Cellulose, NF; Lactose, Hydrous, NF; Croscarmellose Sodium, NF; FD&C Blue No. 2, and Magnesium Stearate, NF.

CLINICAL PHARMACOLOGY: Methazolamide is a potent inhibitor of carbonic anhydrase. Methazolamide is well absorbed from the gastrointestinal tract. Peak plasma concentrations are observed 1 to 2 hours after dosing. In a multiple-dose pharmacokinetic study, administration of methazolamide 25 mg BID, 50 mg BID and 100 mg BID demonstrated a linear relationship between plasma methazolamide levels and methazolamide dose. Peak plasma concentrations (C_{max}) for the 25 mg, 50 mg and 100 mg BID regimens were 2.5 mcg/mL, 5.1 mcg/mL and 10.7 mcg/mL, respectively. The area under the plasma concentration-time curves (AUC) were 1130 mcg.min/mL, 2571 mcg.min/mL and 5418 mcg.min/mL for the 25 mg 50 mg and 100 mg dosage regimens, respectively. Methazolamide is distributed throughout the body including the plasma, cerebrospinal fluid, aqueous humor of the eye, red blood cells, bile and extra-cellular fluid. The mean apparent volume of distribution (V_{area}/F) ranges from 17 to 23 L. Approximately 55% is bound to plasma proteins. The steady-state methazolamide red blood cell: plasma ratio varies with dose and was found to be 27:1, 16:1 and 10:1 following the administration of methazolamide 25 mg BID, 50 mg BID and 100 mg BID, respectively.

The mean steady-state plasma elimination half-life for methazolamide is approximately 14 hours. At steady-state approximately 25% of the dose is recovered unchanged in the urine over the dosing interval. Renal clearance accounts for 20-25% of the total clearance of drug. After repeated BID-TID dosing, methazolamide accumulates to steady state concentration in seven days.

Methazolamide's inhibitory action on carbonic anhydrase decreases the secretion of aqueous humor and results in a decrease in intraocular pressure. The onset of the decrease in intraocular pressure generally occurs within two to four hours, has a peak effect in six to eight hours, and a total duration of ten to eighteen hours.

Methazolamide is a sulfonamide derivative; however, it does not have any clinically significant antimicrobial properties. Although methazolamide achieves a high concentration in the cerebrospinal fluid, it is not considered an effective anticonvulsant.

Methazolamide has a weak and transient diuretic effect therefore use results in an increase in urinary volume, with excretion of sodium, potassium and chloride. The drug should not be used as a diuretic. Inhibition of renal bicarbonate reabsorption produces an alkaline urine. Plasma bicarbonate decreases and a relative, transient metabolic acidosis may occur due to a disequilibrium in carbon dioxide transport in the red cell. Urinary citrate excretion is decreased by approximately 40% after doses of 100 mg every 8 hours. Uric acid output has been shown to decrease 36% in the first 24 hour period.

INDICATIONS AND USAGE: Methazolamide is indicated in the treatment of ocular conditions where lowering intraocular pressure is likely to be therapeutic benefit, such as chronic open-angle glaucoma, secondary glaucoma, and preoperatively in acute angle-closure glaucoma where lowering the intraocular pressure is desired before surgery.

CONTRAINDICATIONS: Methazolamide therapy is contraindicated in situations in which sodium and/or potassium serum levels are depressed, in cases of marked kidney or liver disease or dysfunction, in adrenal gland failure, and in hyperchloremic acidosis. In patients with cirrhosis, use may precipitate the development of hepatic encephalopathy.

Long-term administration of methazolamide is contraindicated in patients with angle-closure glaucoma, since organic closure of the angle may occur in spite of lowered intraocular pressure.

WARNINGS: Fatalities have occurred, although rarely, due to severe reactions to sulfonamide including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias. Hypersensitivity reactions may recur when a sulfonamide is readministered, irrespective of the route of administration.

If hypersensitivity or other serious reactions occur, the use of this drug should be discontinued.

Caution is advised for patients receiving high-dose aspirin and methazolamide concomitantly as anorexia, tachypnea, lethargy, coma and death have been reported with concomitant use of high-dose aspirin and carbonic anhydrase inhibitors.

PRECAUTIONS:

General: Potassium excretion is increased initially upon administration of methazolamide and in patients with cirrhosis or hepatic insufficiency could precipitate a hepatic coma.

In patients with pulmonary obstruction or emphysema, where alveolar ventilation may be

...demonstrated a linear relationship between plasma methazolamide levels and methazolamide dose. Peak plasma concentrations (C_{max}) for the 25 mg, 50 mg and 100 mg BID regimens were 2.5 mcg/mL, 5.1 mcg/mL and 10.7 mcg/mL, respectively. The area under the plasma concentration-time curves (AUC) were 1130 mcg.min/mL, 2571 mcg.min/mL and 5418 mcg.min/mL for the 25 mg 50 mg and 100 mg dosage regimens, respectively. Methazolamide is distributed throughout the body including the plasma, cerebrospinal fluid, aqueous humor of the eye, red blood cells, bile and extra-cellular fluid. The mean apparent volume of distribution (V_{area}/F) ranges from 17 to 23 L. Approximately 55% is bound to plasma proteins. The steady-state methazolamide red blood cell: plasma ratio varies with dose and was found to be 27:1, 16:1 and 10:1 following the administration of methazolamide 25 mg BID, 50 mg BID and 100 mg BID, respectively.

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General: Potassium excretion is increased initially upon administration of methazolamide and in patients with cirrhosis or hepatic insufficiency could precipitate a hepatic coma.

In patients with pulmonary obstruction or emphysema, where alveolar ventilation may be

impaired methazolamide should be used with caution because it may precipitate or aggravate acidosis.

Information for Patients: Adverse reactions common to all sulfonamide derivatives may occur: anaphylaxis, fever, rash (including erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis) crystalluria, renal calculus, bone marrow depression, thrombocytopenic purpura, hemolytic anemia, leukopenia, pancytopenia and agranutocytosis. Precaution is advised for early detection of such reactions and the drug should be discontinued and appropriate therapy instituted.

Caution is advised for patients receiving high-dose aspirin and methazolamide concomitantly.

Laboratory Tests: To monitor for hematologic reactions common to all sulfonamides, it is recommended that a baseline CBC and platelet count be obtained on patients prior to initiating methazolamide therapy and at regular intervals during therapy. If significant changes occur, early discontinuance and institution of appropriate therapy are important. Periodic monitoring of serum electrolytes is also recommended.

Drug Interactions: Methazolamide should be used with caution in patients on steroid therapy because of the potential for developing hypokalemia. Caution is advised for patients receiving high-dose aspirin and methazolamide concomitantly, as anorexia, tachypnea lethargy, coma and death have been reported with concomitant use of high dose aspirin and carbonic anhydrase inhibitors (see WARNINGS).

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to evaluate methazolamide's carcinogenic potential and its effect on fertility have not been conducted. Methazolamide was not mutagenic in the Ames bacterial test.

Pregnancy: Teratogenic effects. Pregnancy Category C. Methazolamide has been shown to be teratogenic (skeletal anomalies) in rats when given in doses approximately 40 times the human dose. There are no adequate and well controlled studies in pregnant women. Methazolamide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from methazolamide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and effectiveness of methazolamide in children have not been established.

ADVERSE REACTIONS: Adverse reactions, occurring most often early in therapy, include paresthesias, particularly a "tingling" feeling in the extremities; hearing dysfunction or tinnitus; fatigue; malaise; loss of appetite; taste alteration; gastrointestinal disturbances such as nausea, vomiting and diarrhea; polyuria; and occasional instances of drowsiness and confusion.

Metabolic acidosis and electrolyte imbalance may occur.

Transient myopia has been reported. This condition invariably subsides upon diminution or discontinuance of the medication.

Other occasional adverse reactions include urticaria, melena, hematuria, glycosuria, hepatic insufficiency, flaccid paralysis, photosensitivity, convulsions, and rarely, crystalluria and renal calculi. Also see PRECAUTIONS: Information for Patients for possible reactions common to sulfonamide derivatives. Fatalities have occurred although rarely due to severe reactions to sulfonamides including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia, and other blood dyscrasias (see WARNINGS).

OVERDOSAGE: No data are available regarding methazolamide overdosage in humans as no cases of acute poisoning with this drug have been reported. Animal data suggest that even a high dose of methazolamide is nontoxic. No specific antidote is known. Treatment should be symptomatic and supportive.

Electrolyte imbalance, development of an acidotic state, and central nervous system effects might be expected to occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Supportive measures may be required to restore electrolyte and pH balance.

DOSAGE AND ADMINISTRATION: The effective therapeutic dose administered varies from 50 mg to 100 mg 2 or 3 times daily. The drug may be used concomitantly with miotic and osmotic agents.

HOW SUPPLIED:

Methazolamide Tablets, USP, 25 mg, are hexagonal, unscored, pale blue, tablets supplied as follows:

BOTTLES OF 100

Methazolamide Tablets, USP, 50 mg, are round, scored, pale blue tablets supplied as follows:

BOTTLES OF 100

Methazolamide is not available for parenteral use.

Store at controlled room temperature 15° - 30°C (59° - 86°F).

CAUTION: Federal (USA) law prohibits dispensing without prescription.

Manufactured By:
APPLIED ANALYTICAL INDUSTRIES, INC.
Wilmington, North Carolina 28405
USA

Rev. 06/97

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Electrolyte imbalance, development of an acidotic state, and central nervous system effects might be expected to occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored.

Supportive measures may be required to restore electrolyte and pH balance.

DOSAGE AND ADMINISTRATION: The effective therapeutic dose administered varies from 50 mg to 100 mg 2 or 3 times daily. The drug may be used concomitantly with miotic and osmotic agents.

HOW SUPPLIED:

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BOTTLES OF 100

Methazolamide Tablets, USP, 50 mg, are round, scored, pale blue tablets supplied as follows:

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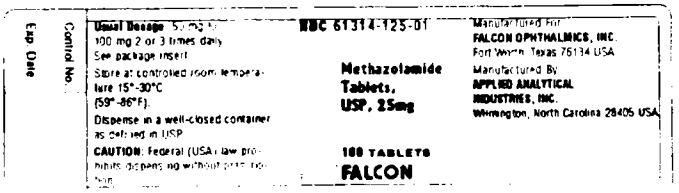
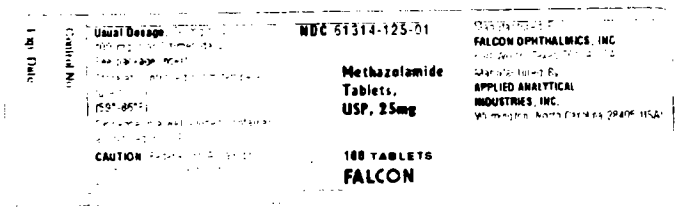
CAUTION: Federal (USA) law prohibits dispensing without prescription.

Manufactured By:
APPLIED ANALYTICAL INDUSTRIES, INC.
Wilmington, North Carolina 28405 USA

Rev. 06/97


Exp. Date
Control No.
Usual Dosage
100 mg 2 or 3 times daily
See package insert
Store at controlled room temperature 15°-30°C (59°-86°F).
Dispense in a well-closed container as defined in USP.
CAUTION: Federal (USA) law prohibits dispensing without
NDC 61314-125-01
Methazolamide Tablets, USP, 25mg
100 TABLETS
FALCON
Manufactured For:
FALCON OPHTHALMICS, INC.
Fort Worth, Texas 76134 USA
Manufactured By:
APPLIED ANALYTICAL INDUSTRIES, INC.
Wilmington, North Carolina 28405 USA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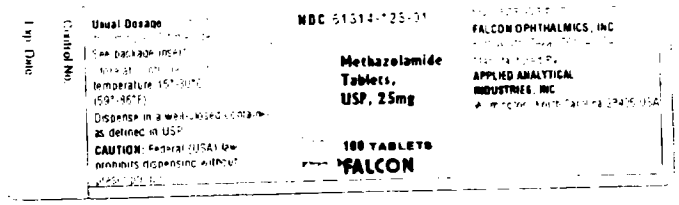
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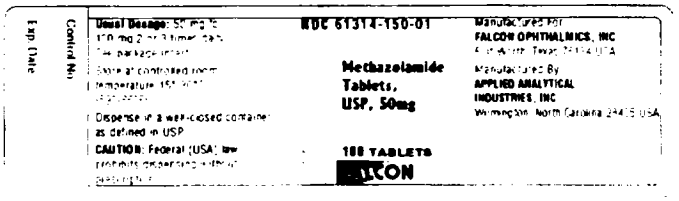
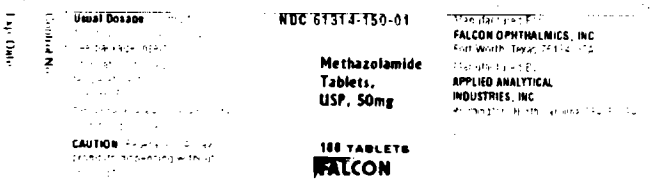

Exp. Date
Control No.
Usual Dosage:
Dispense in a well-closed container as defined in USP
CAUTION: Federal (USA) law
NDC 61314-150-01
Methazolamide
Tablets,
USP, 50mg
100 TABLETS
FALCON
Manufactured for
FALCON OPHTHALMICS, INC
Manufactured By
APPLIED ANALYTICAL
INDUSTRIES, INC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USP, 50mg
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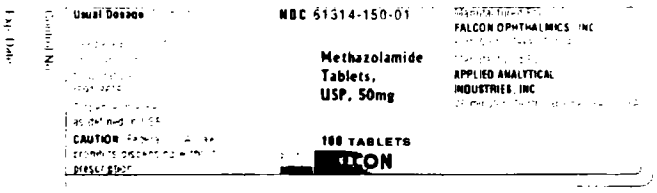
FALCON OPHTHALMICS, INC
APPLIED ANALYTICAL
INDUSTRIES, INC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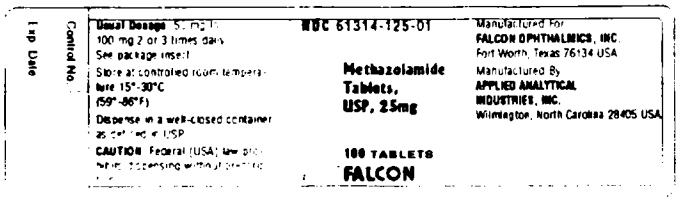
APPLIED ANALYTICAL
INDUSTRIES, INC


Exp Date
Control No.
Usual Dosage
100 mg 2 or 3 times daily
See package insert
Store at controlled room temperature 15°-30°C (59°-86°F)
Dispense in a well-closed container as defined in USP
CAUTION Federal (USA) law prohibits dispensing without prescription
NDC 61314-125-01
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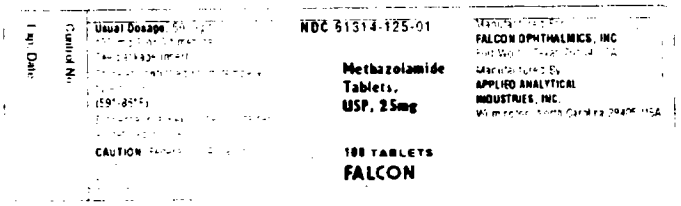
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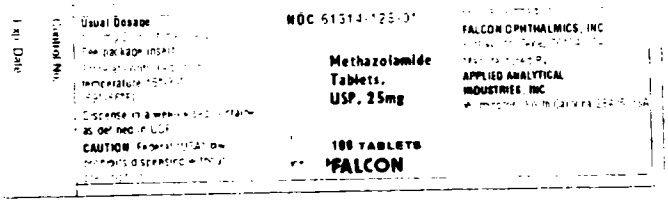
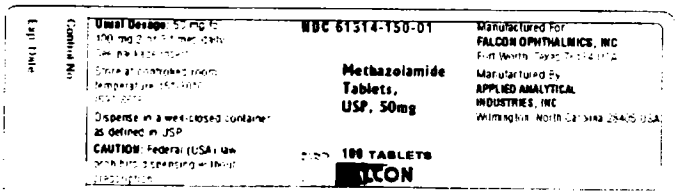
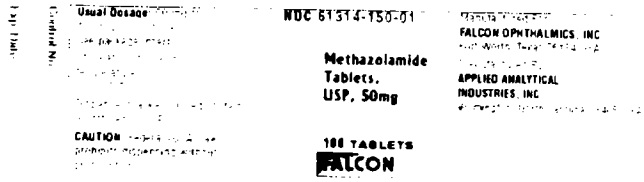
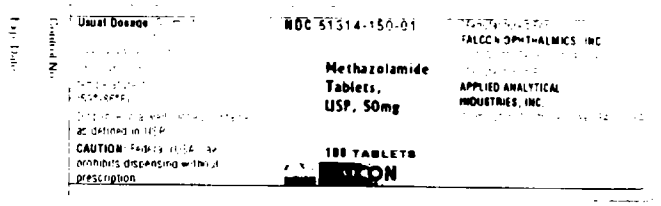
FALCON OPHTHALMICS, INC
APPLIED ANALYTICAL INDUSTRIES, INC.


Exp Date
Control No.
Usual Dosage
See package insert
CAUTION
NDC 61314-125-01
Methazolamide Tablets, USP, 25mg
100 TABLETS
FALCON
FALCON OPHTHALMICS, INC
APPLIED ANALYTICAL INDUSTRIES, INC

MAIL


Usual Dosage
Dispense in a well-closed container as defined in USP
CAUTION: Federal (USA) law prohibits dispensing without prescription
NDC 61314-150-01
Methazolamide Tablets, USP, 50mg
100 TABLETS
FALCON
Manufactured For
FALCON OPHTHALMICS, INC
Manufactured By
APPLIED ANALYTICAL INDUSTRIES, INC


Usual Dosage
CAUTION
NDC 61314-150-01
Methazolamide Tablets, USP, 50mg
100 TABLETS
FALCON
FALCON OPHTHALMICS, INC
APPLIED ANALYTICAL INDUSTRIES, INC


Usual Dosage
as defined in USP
CAUTION
prescription
NDC 61314-150-01
Methazolamide Tablets, USP, 50mg
100 TABLETS
APPLIED ANALYTICAL INDUSTRIES, INC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040011

CHEMISTRY REVIEW(S)

OFFICE OF GENERIC DRUGS
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

1. CHEMISTRY REVIEW NO. 6 (six)

2. ANDA # 40-011

3. NAME AND ADDRESS OF APPLICANT

Applied Analytical Industries, Inc.
1206 N, 23rd Street
Wilmington, NC 28405

4. LEGAL BASIS FOR SUBMISSION **Satisfactory**

Per review CR#1 by M. Shaikh dated 1/3/92.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME None

7. NONPROPRIETARY NAME

Methazolamide Tablets USP, 25mg and 50mg

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

Firm: Original Submission:		4/18/91	
Amendment	#1:	4/30/92	
"	#2:	1/7/93	
"	#3:	11/28/94	
"	#4:	7/25/95	
"	#5:	10/17/96	
"	#6:	1/08/97	
"	#7:	3/24/97	(telephone amendment)
"	#8:	4/10/97	(telephone amendment)
"	#9:	4/15/97	(telephone amendment)
"	#10:	5/8/97	(telephone amendment)
"	#11:	5/12/97	(telephone amendment)
"	#12:	6/23/97	(telephone amendment)

FDA: NA Letter:	1/28/92
" "	8/14/92
" "	4/21/93
NA (Fatal Flaw) Letter:	10/31/93
" Letter:	5/16/95
" "	10/20/95

10. PHARMACOLOGICAL CATEGORY

Carbonic anhydrase inhibitor
(Treament of glaucoma)

11. Rx or OTC

RX

12. RELATED IND/NDA/DMF(s)

[redacted]

13. DOSAGE FORM

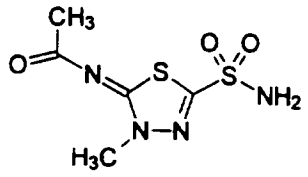
Tablets

14. POTENCY

25mg and 50mg

15. CHEMICAL NAME AND STRUCTURE

Name: Methazolamide
Chemical name: Acetamide, *N*-[5-(aminosulfonyl)-3-methyl-1,3,4-thiadiazol-2(3*H*)-ylidene]-
CAS number: 554-57-4
Molecular weight: 236.28
Chemical formula: $C_5H_8N_4O_3S_2$
Pharmacologic/therapeutic categroy: Carbonic anhydrase inhibitor
Reference: USP 23, page 927
Structural formula:



16. RECORDS AND REPORTS N/A

17. COMMENTS

The current submission, dated January 8, 1997, has stated that the purpose of the submission is to clarify all that has been stated before in earlier amendments and to state that all and only manufacturing, packaging and testing of the finished product will be carried out by [redacted] Previous

amendment-submissions had caused some confusion, but the current submission has now cleared this up.

Our last NA letter, dated 10/20/95, to the applicant indicated th at the only deficiency of the ANDA was lack of acceptable CGMP compliance with the NDS manufacturer and supplier, [redacted] Applicant's amendment, dated 10/17/96, which is the subject of this review, requested an alternate manufacturer, [redacted] Methazolamide USP drug substance.
Amendments reviewed are summarized below:

January 8, 1997
AAI withdrew [redacted] to be a possible packager of the finished product.
AAI withdrew Blister packaging.
AAI withdrew [redacted] to be a possible packaging site.
AAI withdrew [redacted] to be a possible packaging site.

March 24, 1997 (telephone amendment)
AAI withdrew the packaging size of 1000 tablets/bottle.
AAI commits to removing reference to bottles of 1000 in the " How Supplied" section of the labeling.
The 25 mg strength is unscored. On page 148 of the amendment dated October 17, 1996 the word scored was deleted from the description. (AAI admits a human error)
AAI will not market Methazolamide Tablets USP in the bottles of 1000's until such time that three months accelerated stability data are generated and found acceptable.

FDA informed AAI that a pre-approval supplement will be required if the applicant decides to market Methazolamide tablets USP in bottles of 1000's (6/16/97, Record of telephone conversation).

April 10, 1997 and April 15, 1997 (telephone amendments)
AAI proposed batch sizes for the production of Methazolamide Tablets USP 25mg are [redacted] tablets for the 50mg dosage strength. The revised master formula and batch record are provided in the amendments.

May 8, 1997 (telephone amendment)
AAI submitted the certificate of analysis, and dissolution data for the batch of the subject products (lot# 96002 for 25 mg dosage strength, Lot #96003 for 50 mg dosage strength) prepared using the new NDS from [redacted] Dissolution data were satisfactory.

May 12, 1997 (telephone amendment)
AAI clarified the Lot# 96002 and receiving number #96002 on the certificate of analysis provided in the May 8, 1997 submission.

June 23, 1997 (telephone amendment)

AAI stated that the specification sheets and certificates of analysis for the drug products have been amended to remove only the word "alternate" from the ID and assay criteria. Copies of the amended specification sheets and certificates of analysis are appended for both tablet strengths. Submitted information were reviewed and found to be satisfactory.

AAI also submitted a new revision of stability specification concerning related compounds with supporting stability data in the October 17, 1996 submission (PP41-42, 54-57).

18. CONCLUSIONS AND RECOMMENDATIONS

These amendments are **approvable.**

19. REVIEWER: DATE COMPLETED:

Liang-Lii Huang, Ph.D. July 9, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040011

BIOEQUIVALENCE REVIEW(S)

Methazolamide
50 mg Tablet
ANDA # 40-011
Reviewer: Sikta Pradhan
WP #40-011PE

Applied Analytical Industries, Inc.
Wilmington, North Carolina
Submission Date:
April 18, 1991

MAY 13 1991

REVIEW OF A BIOEQUIVALENCY PROTOCOL

In a telephone conversation on May 2, 1991 with Dr. Robert B. Brownfield, Manager, Regulatory Affairs of Applied Analytical Industries, We learned that the in vivo bioequivalence study for Methazolamide 50 mg tablet, manufactured by Applied Analytical, for which this protocol was submitted has already been started. The Division of Bioequivalence, therefore, will not review the protocol. We look forward to reviewing the study data when it is submitted to the Agency.

[redacted]
Sikta Pradhan, Ph. D.
Division of Bioeqivalence
Review Branch I

RD INITIALED ATWU [redacted] 5/6/91
FT INITIALED ATWU

Concur: [redacted]
Ramakant Mhatre, Ph. D.
Acting Deputy Director, Division of Bioequivalence

Date: 5/6/91

cc: ANDA # 40-011 original, HFD-630, HFD-600 (Hare) HFD-22 (Hooton), HFD-652 (Wu, Pradhan), Drug File

Methazolamide Tablet
25 mg and 50 mg
ANDA # 40-011

AUG 13 1992

Dr. Robert B. Brownfield
Manager, Regulatory Affairs
Applied Analytical Industries Inc.
1206 North 23 Street
Wilmington, NC 28405

Dear Dr. Brownfield:

Reference is made to the in vivo bioequivalence study, and waiver request which you submitted on February in support of your methazolamide tablet. 19, 1992

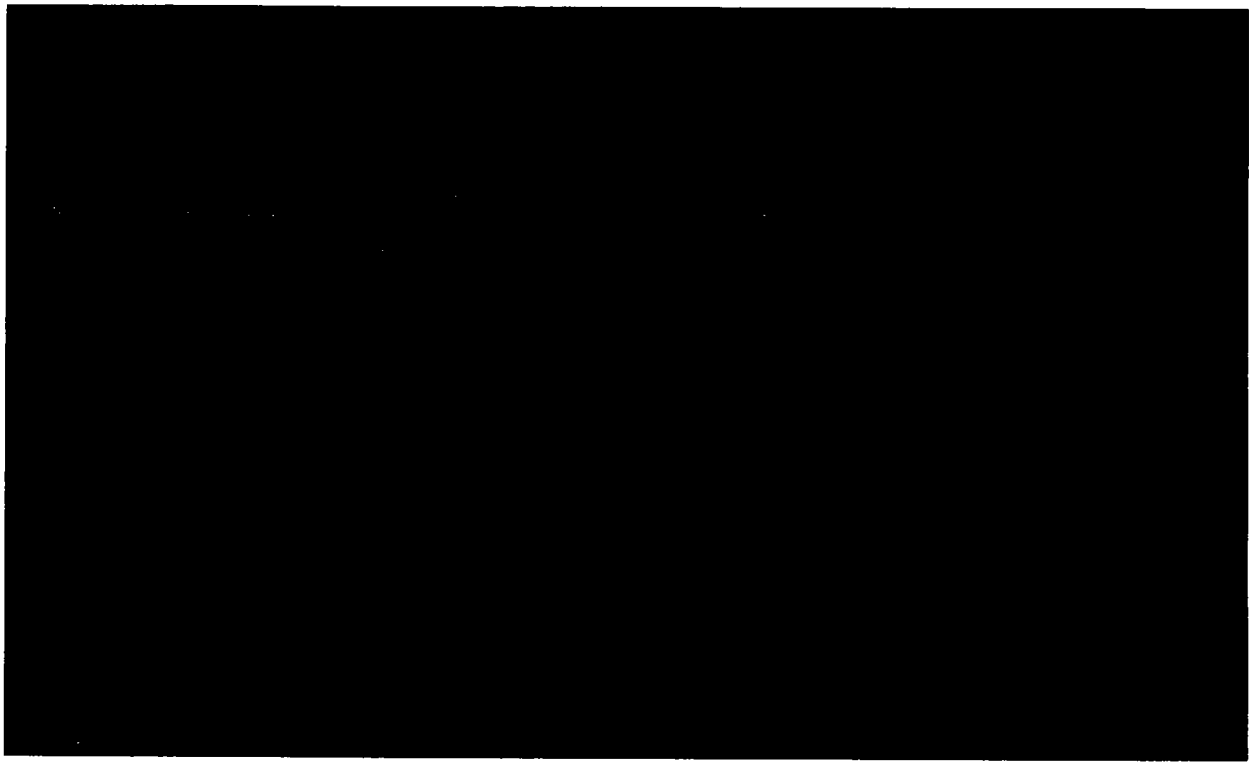
The material has been reviewed by the Division of Bioequivalence and we have the following comments:

DEFICIENCIES:

1.

2.

3.



4. The Agency should be informed whether each blood sample was run in duplicate. The method of calculation of methazolamide in the blood sample should be provided.

5. The laboratory SOP for conducting any repeat analysis of samples should be provided. The data from any repeat analysis should be included in the submission.

RECOMMENDATION:

1. The bioequivalence study conducted by Applied Analytical Industries, Inc. on its test product, methazolamide tablets, 50 mg, lot# 90022B, manufactured by Alcon Laboratories, Inc. comparing it with the reference product, Neptazane® Tablets, 50 mg, lot# 268-383, has been found incomplete by the Division of Bioequivalence due to the deficiencies cited above.

2. The waiver request of in vivo bioequivalence requirements of the test product, 25 mg methazolamide tablets can not be reviewed until the bioequivalence study of the 50 mg strength is found acceptable. The waiver request should be resubmitted with the final report of the in vivo bioequivalence study,

All responses and correspondence with regard to this letter should be sent to the Office of Generic Drugs, HFD-630.

Sincerely yours,

Shrikant V. Dighe, Ph. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

CC: Date _____
HFD-632 Pollock
HFD-650 (Dighe, Greenberg, CST)
stm 07-15-92 (N40011.STD)
bio letter

JUL 10 1992

Methazolamide Tablet
25 mg and 50 mg
ANDA # 40-011
Reviewer: Sikta Pradhan
WP #40011S.292

Applied Analytical Industries,Inc.
Wilmington, North Carolina
Submission Date:
February 19, 1992

REVIEW OF A BIOEQUIVALENCE STUDY AND WAIVER REQUEST

Introduction

Methazolamide, a sulfonamide derivative is white crystalline powder, weakly acidic, and slightly soluble in water. The drug is used in the adjunctive treatment of open-angle glaucoma in an attempt to lower intraocular pressure. The effective therapeutic dose administered in tablet form varies from 50 to 100 mg 2-3 times daily. Several studies in rats demonstrated that the drug causes teratogenic effects at high doses. But there is no evidence of these effects in humans. However, the drug is not recommended for use in women of childbearing potential or during pregnancy. The drug is a potent inhibitor of the enzyme carbonic anhydrase. It binds strongly to carbonic anhydrase in red blood cell. The binding is reversible. After oral administration, drug is absorbed somewhat slowly from GI tract, but it disappears more slowly from the blood producing a prolong drug apparent half life in the blood.

Adverse Reactions reported include anorexia, nausea, vomiting, malaise, fatigue or drowsiness, headache, vertigo,mental confusion, depression and paresthesia of fingers, toes, hands or feet, etc.

Innovator Product

The drug is available as Neptazane[R] (Lederle), 25 and 50 mg Tablets.

In-Vivo Study

Applied Analytical Industries, Inc. has submitted a bioequivalence study on 50 mg Methazolamide Tablet manufactured by Alcon [redacted]

Study Design

A randomized 2-way, crossover,single dose bioequivalence study on the test product, Methazolamide, 50 mg tablet [redacted] and the reference product, Neptazane[R] 50 mg tablet (Lederle) was conducted.

Subject: Thirty (30) male volunteers between 22-48 years of age and within ± 15% of their ideal body weight according to Metropolitan life Insurance Company Bulletin, 1983, were selected for the study after 1) Physical Examination, 2) Medical and Complete Routine Laboratory Test (hematology, blood chemistry, urinalysis, etc.) The subjects were restricted from all medications for two weeks prior to the first drug administration until after the study was completed. The volunteers were not allowed to drink alcoholic beverages for 48 hours prior to the initiation of the study until after the completion of the study. The subjects were randomly divided into two dosing groups of equal numbers.

Treatments:

A. 50 mg x 1 Methazolamide tablet (Alcon), Lot # 90022B
Lot size: [redacted] Potency of the tablet is 100.4%

B. 50 mg x 1 Neptazane^{R} tablet (Lederle), Lot # 268-383,
Potency of the tablet is 99.8%

Dose Administration: A single dose of 50 mg Methazolamide tablet (test or reference) was administered with 180 mL of water.

Drug Washout Period: Two months.

Meal and Food Restrictions: All volunteers fasted for 10 hours prior to and 4 hours after drug administration. Water was given ad lib after two hours of dosing. High protein and low fat containing meal was served. No caffeine-containing food or beverages was served during the first 24 hours.

Blood Samples Collection

Seven (7) mL blood samples were collected in vacutainers containing EDTA at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 10, 12, 24, 30 hours, and 2, 3, 5, 12, 19, 26, 33, 40, 47, 54, 61 days (Table 1). The whole blood was refrigerated for analysis.

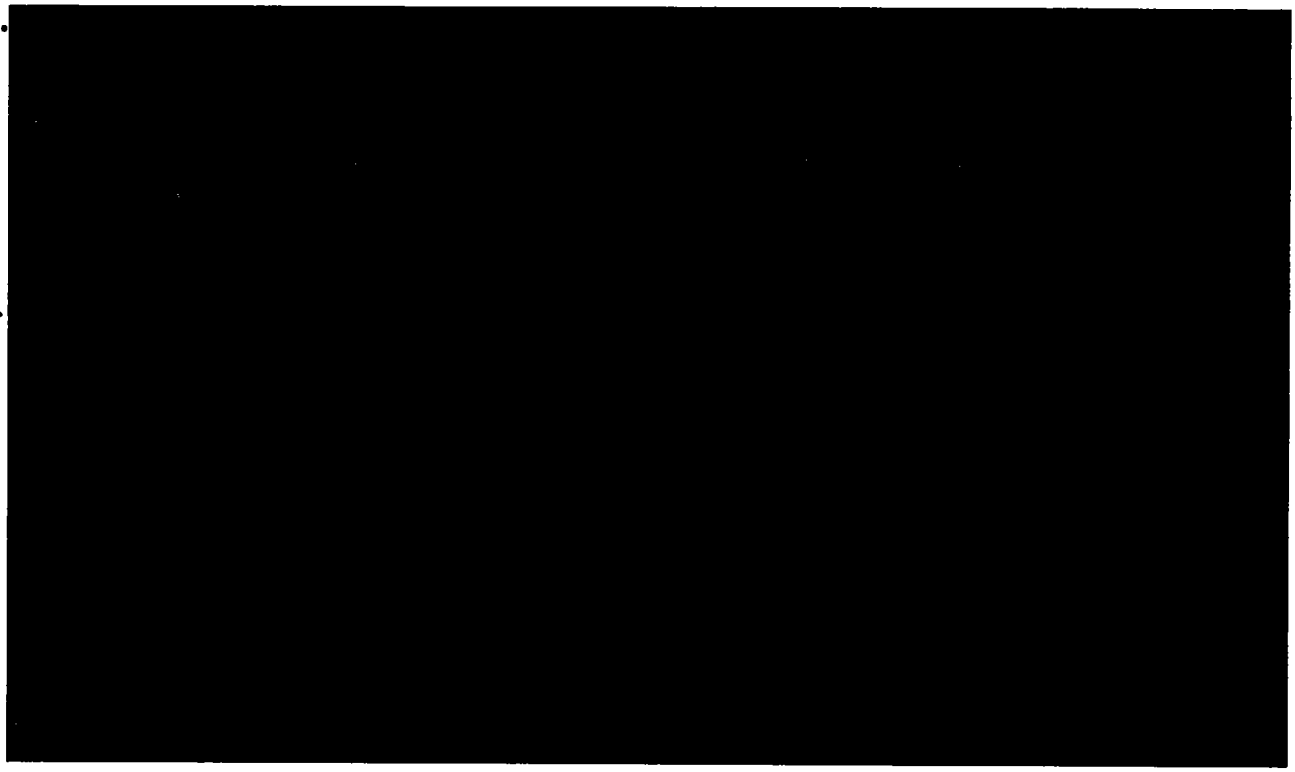
[redacted]

Deficiencies:

1.

2.

3.



4. The firm should inform the Agency whether each blood sample was run in duplicate. The method of calculation of

methazolamide in the blood sample should also be provided.

5. The firm should provide the Laboratory SOP for conducting any repeat analysis of samples. The data of repeat analysis should be included in the submission.

Recommendation:

1. The bioequivalence study conducted by Applied Analytical Industries, Inc. on its test product, Methazolamide Tablets, 50 mg, lot# 90022B, manufactured by [redacted] comparing it with the reference product, Neptazane[R] Tablets, 50 mg, lot# 268-383, has been found incomplete by the Division of Bioequivalence due to the Deficiencies cited above.

2. The waiver request of in vivo bioequivalence requirements of the test product, 25 mg Methazolamide Tablets can not be reviewed until the bioequivalence study of the 50 mg strength is found acceptable.

The firm should be informed of all Deficiencies and Recommendations.

[redacted]

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITIAL [redacted]
FT INITIAL

Concur: [redacted] Date: 7/1/92

Shrikant V. Dighe, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 40-011 original, HFD-600 (Hare), HFD-652 (Wu,Pradhan), HFC-130 (Allen), Drug File.

PD/061292/ntp/061692/WP#40011S.292

JUN 1 1 1993

Methazolamide
50 mg Tablet
ANDA # 40-011
Reviewer: Sikta Pradhan
WP #40011SDW.N92

Applied Analytical Industries, Inc.
Wilmington, North Carolina
Submission Date:
February 19, 1992
November 23, 1992

REVIEW OF A BIOEQUIVALENCE STUDY

Introduction

Methazolamide, a sulfonamide derivative is white crystalline powder, weakly acidic, and slightly soluble in water. The drug is used in the adjunctive treatment of open-angle glaucoma in an attempt to lower intraocular pressure. The effective therapeutic dose administered in tablet form varies from 50 to 100 mg 2-3 times daily. Several studies in rats demonstrated that the drug causes teratogenic effects at high doses. But there is no evidence of these effects in humans. However, the drug is not recommended for use in women of childbearing potential or during pregnancy. The drug is a potent inhibitor of the enzyme carbonic anhydrase. It binds strongly to carbonic anhydrase in red blood cell. The binding is reversible. After oral administration, drug is absorbed somewhat slowly from GI tract, but it disappears more slowly from the blood producing a prolong drug apparent half life in the blood.

Adverse Reactions reported include anorexia, nausea, vomiting, malaise, fatigue or drowsiness, headache, vertigo, mental confusion, depression and paresthesia of fingers, toes, hands or feet, etc.

Innovator Product

The drug is available as Neptazane® (Lederle), 25 and 50 mg Tablets.

In-Vivo Study

Applied Analytical Industries, Inc. has submitted a bioequivalence study on its 50 mg Methazolamide Tablets. The clinical study was

[redacted]

Study Design

A randomized 2-way, crossover,single dose bioequivalence study on the test product, Methazolamide, 50 mg tablet (Applied Analytical) and the reference product, Neptazane^{R} 50 mg tablet (Lederle) was conducted.

Subject: Thirty (30) male volunteers between 22-48 years of age and within ± 15% of their ideal body weight according to Metropolitan life Insurance Company Bulletin, 1983, were selected for the study after 1) Physical Examination, 2) Medical and Complete Routine Laboratory Test (hematology, blood chemistry, urinalysis, etc.) The subjects were restricted from all medications for two weeks prior to the first drug administration until after the study was completed. The volunteers were not allowed to drink alcoholic beverages for 48 hours prior to the initiation of the study until after the completion of the study. The subjects were randomly divided into two dosing groups of equal numbers.

Treatments:

A. 50 mg x 1 Methazolamide tablet (Applied Analytical), Lot #90022B
Lot size: [redacted] Potency of the tablet is 100.4%

B. 50 mg x 1 Neptazane^{R} tablet (Lederle), Lot #268-383, Potency of the tablet is 99.8%

Dose Administration: A single dose of 50 mg Methazolamide tablet (test or reference) was administered with 180 mL of water.

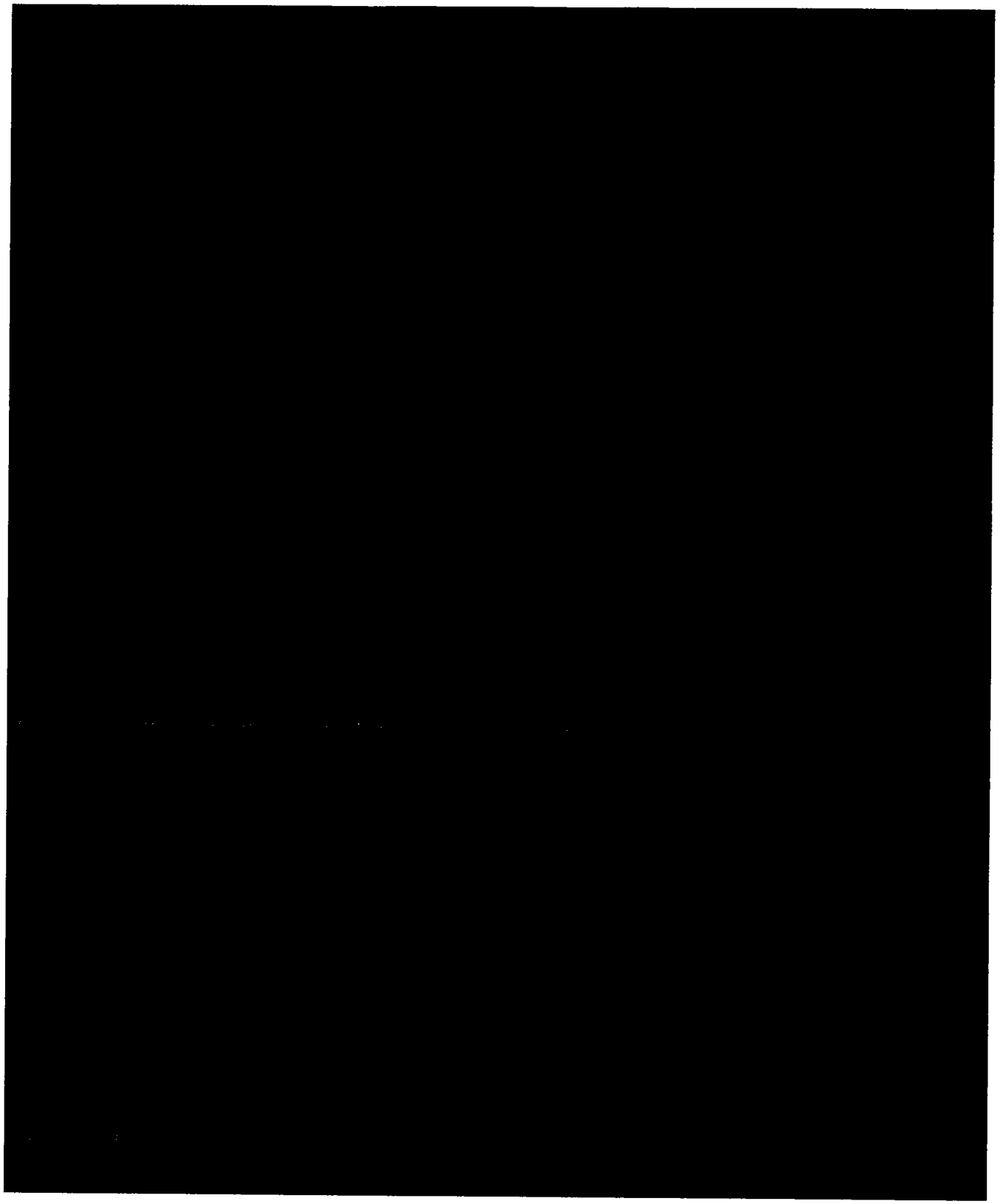
Drug Washout Period: Nine weeks.

Meal and Food Restrictions: All volunteers fasted for 10 hours prior to and 4 hours after drug administration. Water was given ad lib after two hours of dosing. High protein and low fat containing meal was served. No caffeine-containing food or beverages was served during the first 24 hours.

Blood Samples Collection

Seven (7) mL blood samples were collected in vacutainers containing EDTA at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 10, 12, 24, 30 hours, and 2, 3, 5, 12, 19, 26, 33, 40, 47, 54, 61 days (Table 1). The whole blood was refrigerated for analysis.

Assay Methodology



[redacted]

The study results submitted by the firm are attached with this review.

In-Vitro Dissolution:

The firm has conducted an acceptable dissolution testing on Methazolamide tablets using the methodology and criteria of the USP XXII Monograph for Methazolamide Tablets. The USP dissolution medium is Acetate Buffer, pH 4.5 (FDA method recommends 0.1N HCl). The dissolution testing data are presented in Table 3 below:

Drug (Generic Name): Methazolamide Tablets
Dose Strength: 50 mg, 25 mg
ANDA # 40-011

Firm: [redacted]

Submission Date: November 23, 1992

Table -3 In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket __ Paddle X RPM 100 No. Units Tested: 12
Medium: Acetate Buffer Volume: 900 ml
Reference Drug: (Manuf.) Neptazane® 50 mg Tablet (Lederle)
Assay Methodology: [redacted]

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # 90022B Strength (mg) 50 Mean % Dissolved	Range	(CV)	Reference Product Lot # 268-383 Strength (mg) 50 Mean % Dissolved	Range	(CV)
10	104.0	[redacted]	(1.3)	104.0	[redacted]	(2.8)
20	104.1		(1.1)	104.4		(2.7)
30	103.8		(1.0)	104.4		(2.7)
45	104.0		(0.9)	104.4		(2.7)
INFINITY	104.0		(1.0)	103.8		(2.6)

Sampling Times (Min.)	Test Product Lot # 90021B Strength (mg) 25 Mean % Dissolved	Range	(CV)	Reference Product Lot # 294-484 Strength (mg) 25 Mean % Dissolved	Range	(CV)
10	101.3	[redacted]	(3.4)	99.8	[redacted]	(2.7)
20	101.4		(3.5)	103.0		(1.7)
30	101.6		(3.4)	103.1		(1.8)
45	101.6		(3.5)	102.9		(1.6)
INFINITY	102.1		(3.5)	103.2		(1.7)

The firm has also conducted the comparative dissolution testing using USP paddle at 50 rpm and at 75 rpm. The mean dissolution testing data for 25 mg and 50 mg test and reference tablets are presented below:

	Mean (%) Dissolved			
	Test Tablets		Reference Tablets	
	25 mg	50 mg	25 mg	50 mg
Paddle at 50 rpm:				
10 min.	79.0	77.8	33.3	30.1
20 min.	87.6	86.8	42.9	41.7
30 min.	91.5	89.5	50.6	47.2
45 min.	94.6	91.7	61.2	55.3
Infinity	102.4	101.0	104.6	101.4
Paddle at 75 rpm:				
10 min.	101.1	98.2	93.0	81.4
20 min.	101.4	101.0	101.6	93.3
30 min.	101.9	101.3	103.6	97.0
45 min.	101.9	101.6	104.8	98.8
Infinity	102.2	101.7	106.1	101.0

Comments:

1. The in vitro dissolution testing conducted on 50 mg and 25 mg Methazolamide Tablets is acceptable.

2. The in vivo bioequivalence study conducted on the test and the reference products has been found unacceptable due to the deficiencies cited below.

Deficiencies:

1. [redacted]

2. [redacted]

3.

4.

Recommendations:

1. The bioequivalence study conducted by Applied Analytical Industries, Inc. on its test product, Methazolamide Tablets, 50 mg, lot# 90022B, comparing it with the reference product, Neptazane[R] Tablets, 50 mg, lot# 268-383, has been found unacceptable to the Division of Bioequivalence due to the Deficiencies cited above.

2. The waiver request of <u>in vivo</u> bioequivalence requirements of the test product, 25 mg Methazolamide Tablets can not be reviewed until the bioequivalence study of the 50 mg strength is found acceptable.

The firm should be informed of all Deficiencies and Recommendations.

[redacted]

Sikta Pradhan, Ph. D.
Division of Bioequivalence
Review Branch I

RD INITI[redacted]
FT INITI

Concur: [redacted] Date: 6/11/93

Ramakant M. Mhatre, Ph.D.
Acting Director, Division of Bioequivalence

cc: ANDA # 40-011 original, HFD-600 (Hare), HFD-652 (Wu,Pradhan), HFC-130 (Allen), Drug File.

SP/060193/ntp/060293/WP #40011SDW.N92

SUMMARY OF BIOEQUIVALENCE DATA

Attached are the following tables which summarize the bioequivalence data:

1. Summary of Statistical Analysis
2. Individual and Mean Whole Blood Concentrations for the Test Product
3. Individual and Mean Whole Blood Concentrations for the Reference Product

Summary of statistical analysis for methazolamide whole blood pharmacokinetic parameters comparing Treatments A and B

PARAMETER	UNITS	TREAT A	TREAT B	PCT DIFFERENCE	TWO ONE-SIDED 'T' ANALYSIS
CMAX	ng/mL	9639	9341	3.19	96.7 - 109.6
TMAX	hr	6.93	10.22	-32.19	-10.7 - 146.3
LCMAX		9.16	9.12	.	97.7 - 110.6
LAUC		14.85	14.81	.	97.2 - 111.9

Treatment A = 50 mg methazolamide tablet (Applied Analytical)
Treatment B = 50 mg Neptazane(R) tablet (Lederle Laboratories)

Values for Treatments A and B are the least-square means (LSMEANS) from the ANOVA
LCMAX and LAUC are log-transformed parameters
. = value was not calculated

PCT DIFFERENCE = difference between treatments (A - B) expressed as a percentage of treatment B

TWO ONE-SIDED 'T' ANALYSIS = shortest confidence intervals (90% confidence)

APPLIED ANALYTICAL INDUSTRIES, INC.
METHAZOLAMIDE STUDY #14751

Individual and mean methazolamide whole blood
concentrations (ng/mL) for 50 mg methazolamide tablet (Applied Analytical)

SUBJ	0.0 hr	0.5 hr	1.0 hr	1.5 hr	2.0 hr	2.5 hr	3.0 hr	4.0 hr	6.0 hr	10.0 hr	12.0 hr	24.0 hr	30.0 hr	48.0 hr	72.0 hr
2	[redacted]														
3															
5															
7															
8															
9															
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MEAN	0	5491	7442	8125	8470	8566	8684	8590	8405	8309	8459	8208	7938	7616	7008
STD. DEV.	0	3072	2580	2245	1959	1581	1675	1566	1386	1411	1339	1196	1419	1596	1270
C.V.(%)	0	56.0	34.7	27.6	23.1	18.5	19.3	18.2	16.5	17.0	15.8	14.6	17.9	21.0	18.1
S.E.M.	0	614	516	449	392	316	335	313	277	282	268	239	284	326	259
N	25	25	25	25	25	25	25	25	25	25	25	25	25	24	24
MIN	BQL	BQL	2365	3757	4653	4968	5733	5786	5064	5276	5212	5437	5427	3361	4528
MAX	BQL	10705	12592	14176	11454	11376	12832	12276	10982	11127	10784	10320	11196	10728	9258

BQL = below quantifiable limits; NR = not reported

(5)

APPLIED ANALYTICAL INDUSTRIES, INC.
METHAZOLAMIDE STUDY #14751

Individual and mean methazolamide whole blood concentrations (ng/mL) for 50 mg methazolamide tablet (Applied Analytical)

SUBJ	120.0 hr	288.0 hr	456.0 hr	624.0 hr	792.0 hr	960.0 hr	1128.0 hr	1296.0 hr	1464.0 hr
2	[redacted]								
3									
5									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
18									
19									
20									
21									
22									
23									
25									
26									
27									
28									
29									
30									
MEAN	5980	4148	2814	1707	738	197	134	114	0
STD. DEV.	1097	741	669	1074	934	544	465	571	0
C.V.(%)	18.3	17.9	23.8	62.9	127	276	347	500	0
S.E.M.	229	148	137	215	187	109	93	114	0
N	23	25	24	25	25	25	25	25	25
MIN	4632	3064	1977	BQL	BQL	BQL	BQL	BQL	BQL
MAX	9951	5606	4366	3384	2248	1673	1780	2853	BQL

BQL = below quantifiable limits; NR = not reported

16

APPLIED ANALYTICAL INDUSTRIES, INC.
METHAZOLAMIDE STUDY #14751

Individual and mean methazolamide whole blood concentrations (ng/mL) for 50 mg Neptazane(R) tablet (Lederle Laboratories)

SUBJ	0.0 hr	0.5 hr	1.0 hr	1.5 hr	2.0 hr	2.5 hr	3.0 hr	4.0 hr	6.0 hr	10.0 hr	12.0 hr	24.0 hr	30.0 hr	48.0 hr	72.0 hr
2	[redacted]														
3															
5															
7															
8															
9															
10															
11															
12															
13															
14															
15															
16															
18															
19															
20															
21															
22															
23															
25															
26															
27															
28															
29															
30															
MEAN	0	3846	6150	7481	7822	8483	8607	8523	8111	8324	7888	7768	7462	7476	7095
STD. DEV.	0	3140	3502	2895	2431	2191	1923	1677	1647	1975	1524	1300	1105	1824	1855
C.V.(%)	0	81.6	56.9	38.7	31.1	25.8	22.3	19.7	20.3	23.7	19.3	16.7	14.8	24.4	26.1
S.E.M.	0	628	700	579	486	438	385	335	329	395	305	260	221	365	379
N	25	25	25	25	25	25	25	25	25	25	25	25	25	25	24
MIN	BQL	BQL	BQL	BQL	1946	3631	5217	6470	5850	6027	5706	5789	5723	4834	4312
MAX	BQL	11392	13063	12916	12460	12488	12768	12884	12074	14060	10959	10888	9996	10974	12565

BQL = below quantifiable limits; NR = not reported

APPLIED ANALYTICAL INDUSTRIES, INC.
METHAZOLAMIDE STUDY #14751

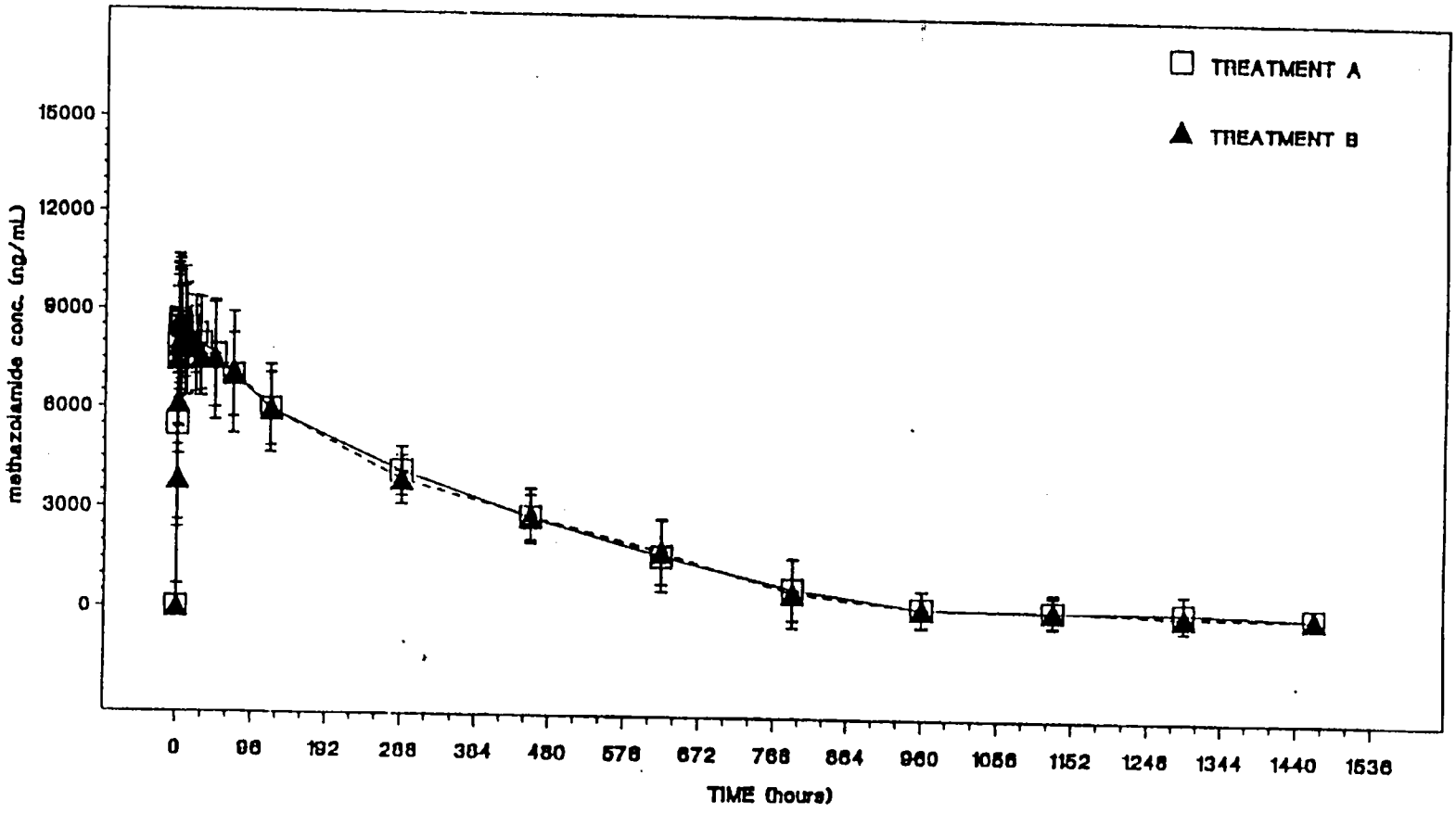
Individual and mean methazolamide whole blood
concentrations (ng/mL) for 50 mg Neptazane(R) tablet (Lederle Laboratories)

SUBJ	120.0 hr	288.0 hr	456.0 hr	624.0 hr	792.0 hr	960.0 hr	1128.0 hr	1296.0 hr	1464.0 hr
2	[redacted]								
3									
5									
7									
8									
9									
10									
11									
12									
13									
14									
15									
16									
18									
19									
20									
21									
22									
23									
25									
26									
27									
28									
29									
30									
MEAN	5990	3889	2854	1838	620	168	152	0	0
STD. DEV.	1330	730	813	977	1053	581	525	0	0
C.V.(%)	22.2	18.8	28.5	53.2	170	346	346	0	0
S.E.M.	266	146	166	195	211	116	105	0	0
N	25	25	24	25	25	25	25	24	25
MIN	3506	2575	1635	BQL	BQL	BQL	BQL	BQL	BQL
MAX	9417	5500	5196	3930	3122	2114	1904	BQL	BQL

BQL = below quantifiable limits; NR = not reported

APPLIED ANALYTICAL INDUSTRIES, INC.
METHAZOLAMIDE STUDY #14751
TREAT A = 50 mg methazolamide tablet (Applied Analytical)
TREAT B = 50 mg Neptazane(R) tablet (Lederle Laboratories)
methazolamide in whole blood

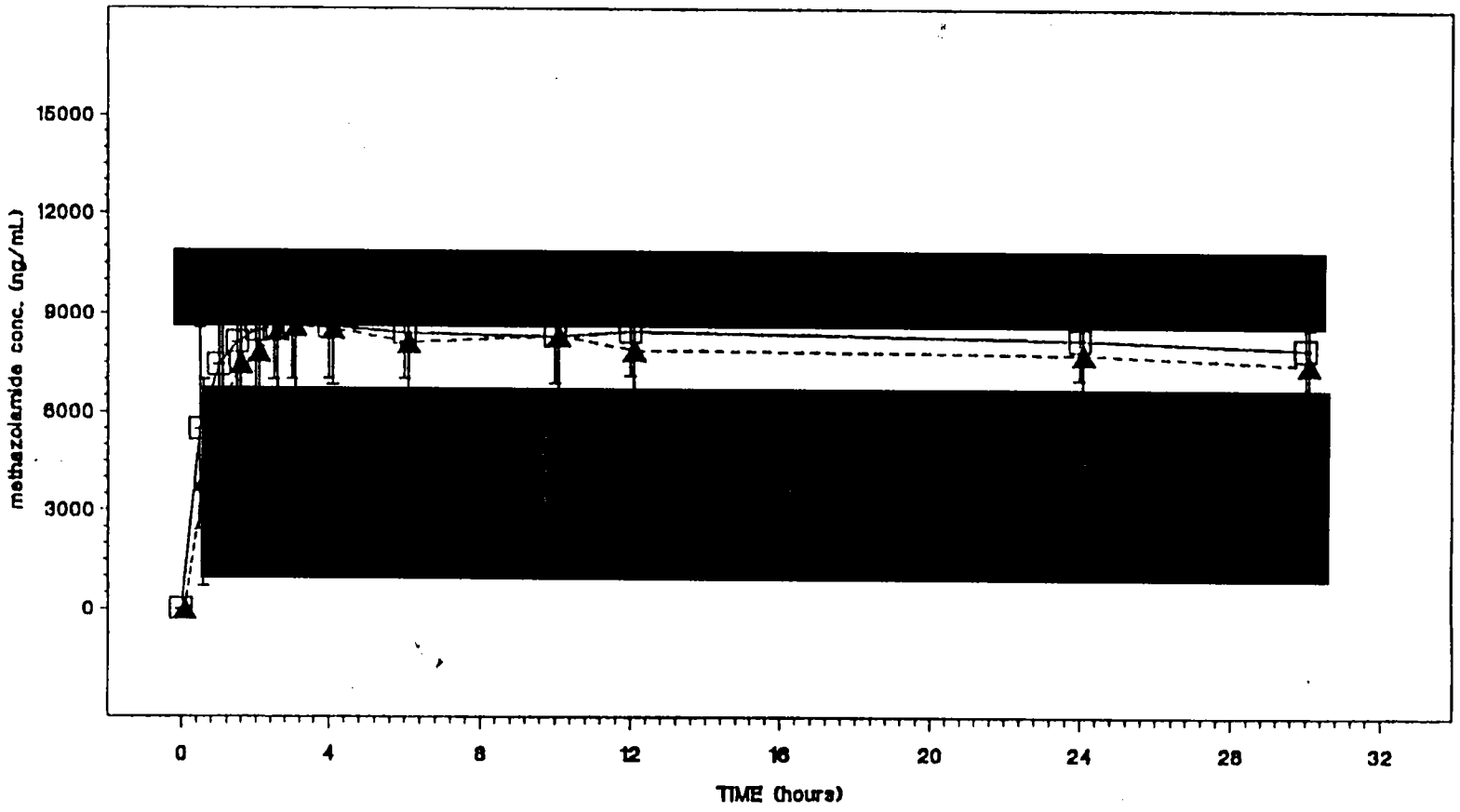
MEAN (S.D.) OF ALL SUBJECTS



LINEAR SCALE
TREATMENT B HAS BEEN OFFSET 0.1 HOURS TO FACILITATE VIEWING

APPLIED ANALYTICAL INDUSTRIES, INC.
METHAZOLAMIDE STUDY #14751
TREAT A = 50 mg methazolamide tablet (Applied Analytical)
TREAT B = 50 mg Neptazane(R) tablet (Lederle Laboratories)
methazolamide in whole blood

MEAN (S.D.) OF ALL SUBJECTS



LINEAR SCALE
TREATMENT B HAS BEEN OFFSET 0.1 HOURS TO FACILITATE VIEWING

FORMULATION

Methazolamide Tablets USP, 50mg

Ingredient	%W/W	mg/tablet
Methazolamide USP	26.15	50.0
Microcrystalline Cellulose NF	31.38	60.0
Lactose Hydrous NF	31.38	60.0
Croscarmellose Sodium NF	10.46	20.0
Magnesium Stearate NF	0.53	1.02
FD&C Blue No. 2 [redacted] Lake (13%)	0.10	0.191
Total	100.0%	191.2 mg

APPENDIX C
System Precision

1000 ng/mL Extracted Blood Standard

Sample	Peak Height of Methazolamide	Peak Height of Internal Standard	Ratio
1	[redacted]		
2			
3			
4			
5			
6			
7			
8			
9			
10			
		MEAN	0.34363
		SD	0.015224
		RSD	4.4%

Laboratory Notebook Reference: Applied Analytical Industries
Page M7880019A

APPENDIX E
Method Precision
Methazolamide in Whole Blood
Linearity Standards and Controls

DAY 1 DAY 2

[redacted]

Response Factor (Conc (ng/mL)) (m)

Laboratory Notebook Reference: Applied Analytical Industries
Pages VD24002-3A

CONTROL DATA LIST

Attached are the data for the control samples which were run on a daily basis as part of the assay of the blood samples. As described in Section IX.A.1.g., variability in the control samples was an issue which was discovered when the data were compiled. This variability led to the reassay of some of the blood samples and to the reevaluation of the concentration levels used for the controls. Data are presented for Period 1, Period 2 and the Reassay Period. The data are tabulated by the date. Concentration designations and actual concentration values for the control samples for each period are shown in the table below.

Concentration	Period 1	Period 2	Reassay Period
Low	[redacted]		
Low/Medium			
Medium			
Medium/High			
High			

METHAZOLAMIDE BIOEQUIVALENCE STUDY
"Quality Control" Sample Summary
P E R I O D O N E

Std. Date	LOW, 760.5 ng/mL Found	MID, 7605.0 ng/mL Found	HIGH, 30420.0 ng/mL Found
10/10/90	1137.5	9250.4	36421.5
	1215.8	10155.7	35074.8
	1228.8	6944.9	36883.0
10/11/90	598.0	6393.7	25059.7
	614.6	6347.9	24718.8
10/16/90	580.4	7893.9	32155.4
	539.4	8457.2	31880.3
	518.6	7279.8	26671.3
10/18/90	1206	7448	27563
10/19/90	796	7218	26849
	767	7112	27101
	772		
10/20/90	891	7030	25315
	885	6881	25933
	884	7190	27522
10/22/90	899	5856	30344
	816	7351	21232
	848	7831	30903
10/24/90	924	7776	27024
	965	7170	27255
	925	7130	25772
	916	7101	25417
			27123
10/26/90	395	7252	30173
	437	8259	33407
	404	7529	36532
	412	7491	27219
	548	7706	30657
	432		
10/27/90	412	7529	36532
	548	7491	27219
	432	7706	30657
10/29/90	685	7427	23803
	548	6392	
	734	7143	
	553	8107	
10/31/90	749	7908	29118
	761	7968	28546
	842	8346	32264
	765	8355	32088
11/01/90	789	7738	30133
	832	7045	27445
	835	7023	28858
	855	7524	27722
	841		
11/02/90	655	7724	28524
	848	8173	30174
	753	9631	30143
	754	8327	30198
	739	8241	
11/05/90	70	8556	33887
	54	7934	29078
	24	7962	30979
	17	8032	32009
		7665	

METHAZOLAMIDE BIOEQUIVALENCE STUDY
"Quality Control" Sample Summary
PERIOD ONE
(continued)

Std. Date	LOW, 760.5 ng/mL	MID, 7605.0 ng/mL	HIGH, 30420.0 ng/mL
	Found	Found	Found
11/08/90	647	6357	22622
	715	5980	20227
	737	7246	20451
	793	5626	22261
		6864	
11/12/90	772	7613	32406
	613	820	35052
	578	13676	29430
	680	8126	12010
11/13/90-A	949	6957	25045
	962	7024	27694
	945	6849	27551
	917	6835	28899
11/14/90	561	8699	21078
	514	8612	32247
	661	7740	31620
	516	7930	30938
11/15/90	229	5350	20528
	384	6498	23771
	397	6962	28039
	368	6490	24619
11/16/90	758	9650	30927
	775	8379	32204
	708	8281	31836
	807	7771	31430
		7013	
11/19/90	445	6702	20055
	597	6472	25862
	615	6649	24663
	426	6466	24526
11/19/90-A	659	7458	32022
	709	6109	32683
	266	6842	25998
	640	5982	25507
11/20/90	917	7764	26508
	928	6892	24706
	833	6397	24722
	862	6936	26626
11/20/90-A	19	7821	33835
	297	8439	36298
	67	7534	32566
	31	7471	32639
11/21/90	986	8806	40463
	1058	8961	34343
	904	7923	32871
	995	7669	35593
11/24/90	1068	7126	27289
	1043	7077	25734
	1013	6907	25122
	1124	6898	24353
11/27/90	970	8218	36553
	449	7579	32627
	350	7030	33851
11/27/90-A	720	8614	32581

METHAZOLAMIDE BIOEQUIVALENCE STUDY
"Quality Control" Sample Summary
P E R I O D O N E
(continued)

	LOW, 760.5 ng/mL	MID, 7605.0 ng/mL	HIGH, 30420.0 ng/mL
Std. Date	Found	Found	Found
11/28/90	822	7455	25562
	768	7360	25977
	527	6939	26085
		7124	
11/29/90	747	7523	32548
	656	6982	27664
	559	6216	26257
11/30/90	640	7108	24462
	530	5551	26277
	547	11127	24778
		9539	
11/30/90-A	1060	5973	23761
	1021	6711	21612
	1028	6251	24752
		6373	
12/03/90-A	737	8124	29412
	640	7813	31999
	651	7585	33321
		7444	
12/04/90	473	7247	28161
	569	4915	28576
	596	7072	27770
12/04/90-A	410	9278	47967
	652	8893	32369
12/05/90	3244	8558	33402
	8774	9167	32035
12/05/90-A	4909	6932	29457
	5560	9960	29152
	5089	8178	27371
12/06/90	549	7838	27391
	406	7702	33575
	570	7305	25924
12/06/90-A	476	7576	31951
	566	7555	32540
	523	7764	32339
Average	783	6903	26475

METHAZOLAMIDE BIOEQUIVALENCE STUDY
"Quality Control" Sample Summary
P E R I O D T W O

	LOW, 754.0 ng/mL	MID, 7544.0 ng/mL	HIGH, 30177 ng/mL
Std. Date	Found	Found	Found
01/15/91	243	8515	28536
	235	7711	26921
	205	7133	26625
01/16/91	-15	7809	27878
	-9	7618	25480
	-17	6153	24418
01/16/91-A	505	7362	20814
	489	6965	24353
	497	6487	23973
01/17/91	446	9368	32474
	406	8152	32020
	430	8483	29489
01/17/91-A	-36	8443	26794
	-94	6372	27622
	-128	7883	24158
01/18/91	453	7563	28176
	462	7711	25823
	430	6734	24213
01/18/91-A	300	7709	27643
	275	8584	29659
	264	7300	28249
01/21/91	311	7300	28519
	301	6902	27269
	295	7214	25517
01/21/91-A	110	10208	34082
	90	8604	29965
	71	8328	28528
01/22/91	113	7896	31595
	124	7554	30555
	129	7750	27631
01/23/91	128	8052	30380
	98	7657	28535
	54	7323	28971
01/23/91-A	-76	9009	32076
	-85	8487	33535
	-116	7467	33485
01/24/91	489	9298	27542
	522	8843	25264
	534	8417	22179
01/25/91	-357	7383	26054
		7035	30485
		6519	27707
01/25/91-A	232	7081	26060
		6125	23780
		6003	25083
01/28/91	234	7349	30548
	226	7877	27163
	181	6842	27730
		6838	
01/29/91	153	7686	31882
	135	6564	26450
	121	6915	30458
		6144	

METHAZOLAMIDE BIOEQUIVALENCE STUDY
"Quality Control" Sample Summary
P E R I O D T W O
(continued)

	LOW, 754.0 ng/mL	MID, 7544.0 ng/mL	HIGH, 30177 ng/mL
Std. Date	Found	Found	Found
01/30/91	157	7107	29551
	99	7316	28130
	74	6539	27878
		6832	
01/30/91-A	52	7859	29858
	60	7209	27858
	43	7147	24898
01/31/91	972	7848	22128
	808	7430	24512
	784	7584	24160
		7728	
02/01/91	160	8125	29725
	99	7761	24081
	87	7721	29947
		8171	
02/01/91-A	172	7903	32595
	121	8304	27921
	35	8543	26972
02/05/91	309	7764	28045
	305	7471	21748
	356	7775	32959
03/19/91	574	6932	30078
	517		
03/20/91	526	6713	31397
	511	6588	28133
	553	6880	32723
	592	7284	
		8100	
03/21/91	523	6394	31227
	347	6637	27357
	356	5954	26307
03/25/91	776	6086	28517
	726	6095	23866
	764	6303	22098
	753	5861	24091
03/25/91-A	196	8236	44482
	158	9463	46818
	203		
03/26/91	488	5875	35706
	446	6971	36336
	376	6739	36282
03/28/91	259	8665	32216
	241	7117	31746
	192	6549	34474
	196	6641	31999
04/01/91	202	7718	30665
	262	9000	30737
	225	7877	34444
	243	7898	35072
04/01/91-A	483	7192	29609
	397	7067	30881
	431	7390	23729

METHAZOLAMIDE BIOEQUIVALENCE STUDY
"Quality Control" Sample Summary
P E R I O D T W O
(continued)

	LOW, 754.0 ng/mL	MID, 7544.0 ng/mL	HIGH, 30177 ng/mL
Std. Date	Found	Found	Found
04/02/91	575	8221	29631
	613	7874	29229
	635	8308	27383
04/02/91-A	324	5989	32490
	339	10182	44340
	370	9765	41349
	440	9939	38217
04/03/91	240	7562	30354
	282	7308	28485
	275	7118	32290
04/04/91	99	9756	35511
	100	8710	37599
	34	6452	35469
	92		32218
04/04/91-A	73	8288	35006
	146	7014	28039
	185	7977	29382
04/05/91	460	7130	30843
	437	7545	31328
	453	7765	32122
04/05/91-A	254	7712	28802
	338	8147	32390
	238	8125	32011
	276	9376	31198
04/08/91	129	9274	34742
	127	9572	35924
	66	8129	41613
Average	263	7170	27987

AUG 15 1995

Methazolamide
25 mg and 50 mg Tablets
ANDA # 40-011
Reviewer: Sikta Pradhan, Ph.D.
WP #40011SDW.N94

AAI, Inc.
Wilmington, NC
Submission Date:
Novamber 28, 1994
July 18, 1995

REVIEW OF A BIOEQUIVALENCE STUDY AND WAIVER REQUEST

Introduction

Methazolamide, a sulfonamide derivative, is white crystalline powder, weakly acidic, and slightly soluble in water. The drug is used in the adjunctive treatment of open-angle glaucoma in an attempt to lower intraocular pressure. The effective therapeutic dose administered in tablet form varies from 50 to 100 mg 2-3 times daily. Several studies in rats demonstrated that the drug causes teratogenic effects at high doses. But there is no evidence of these effects in humans. However, the drug is not recommended for use in women of childbearing potential or during pregnancy. The drug is a potent inhibitor of the enzyme carbonic anhydrase. At 25 mg to 50 mg dose, about 96% of the drug binds strongly to carbonic anhydrase in red blood cells. The binding is reversible. After oral administration, drug is absorbed somewhat slowly from GI tract, but it disappears more slowly from the blood producing a prolong ($\simeq$ 15 days) drug apparent half life in the blood.

The drug is currently available as Neptazane^R (Lederle), 25 and 50 mg Tablets. The reported adverse reactions include anorexia, nausea, vomiting, malaise, fatigue or drowsiness, headache, vertigo,mental confusion, depression and paresthesia of fingers, toes, hands or feet, etc.

Objective:

The objective of the study is to compare the relative bioavailability of Methazolamide 50 mg tablets, manufactured by Applied Analytical Industries, Inc., with that of Neptazane^R 50 mg tablets, manufactured by Lederle, in healthy, male volunteers dosed under fasting condition.

In-Vivo Study

Applied Analytical Industries, Inc. had previously submitted (dated February 19, 1992) a randomized two-way crossover, single dose bioequivalence study (Protocol #B-01032) on the test product, Methazolamide, 50 mg tablet (AAI) and reference product, Neptazane^R 50 mg tablet manufactured by Lederle Laboratories, Inc. The study was found unacceptable to the Division of Bioequivalence.

The current bioequivalence study (submission dated November 28, 1994) conducted on the same test product of a newly manufactured batch replaces the previous study.

[redacted]

Study Dates: Clinical Study Initiated -June 25, 1994
Completed -August 5, 1994
Samples Shipped -August 8, 1994
Sample analysis -Initiated -August 30, 1994
Completed -September 20, 1994

Study Design

A randomized, one-period, non-crossover parallel design, single dose bioequivalence study on the test product, Methazolamide, 50 mg tablet (AAI) and the reference product, Neptazane^{R} 50 mg tablet (Lederle) was conducted according to the protocol #B-02024.

Subject: Fifty (50) male volunteers between 18-44 years of age and within ± 10% of their ideal body weight according to Metropolitan life Insurance Company Bulletin, 1983, were selected for the study after 1) Physical Examination, 2) Medical and Complete Routine Laboratory Test (hematology, blood chemistry, urinalysis, etc.) The subjects were restricted from all medications for two weeks prior to the first drug administration until after the study was completed. The volunteers were not allowed to drink alcoholic beverages for 72 hours prior to the initiation of the study until after the completion of the study. The subjects were randomly divided into two dosing groups of equal numbers.

Treatments:

A. 50 mg x 1 Methazolamide tablet (AAI), Lot #94106B, Lot size [redacted] tablets, Potency of the tablet is 98.2%

B. 50 mg x 1 Neptazane^{R} tablets (Lederle), Lot #370-436, Potency of the tablet is 98.1%, Exp. Date: Jannary, 1999

Dose Administration:

A single dose of 50 mg Methazolamide tablets (test or reference) was administered with 8 oz of water. A mouth check was performed to assure ingestion.

Vital signs (resting blood pressure and pulse rate) were recorded

at baseline, and at 4, 8, 12, and 984 hours post-dose. No clinically significant changes were observed in vital signs during the study.

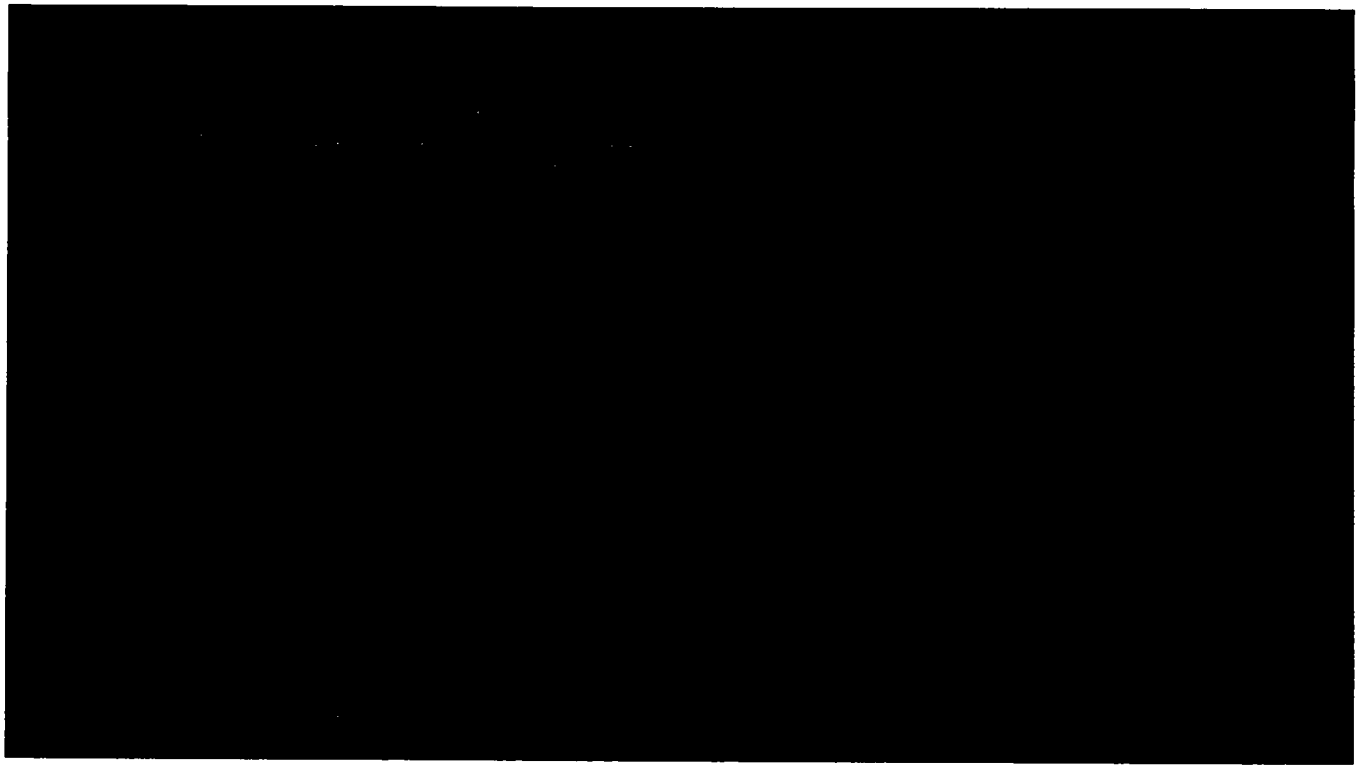
Meal and Food Restrictions:

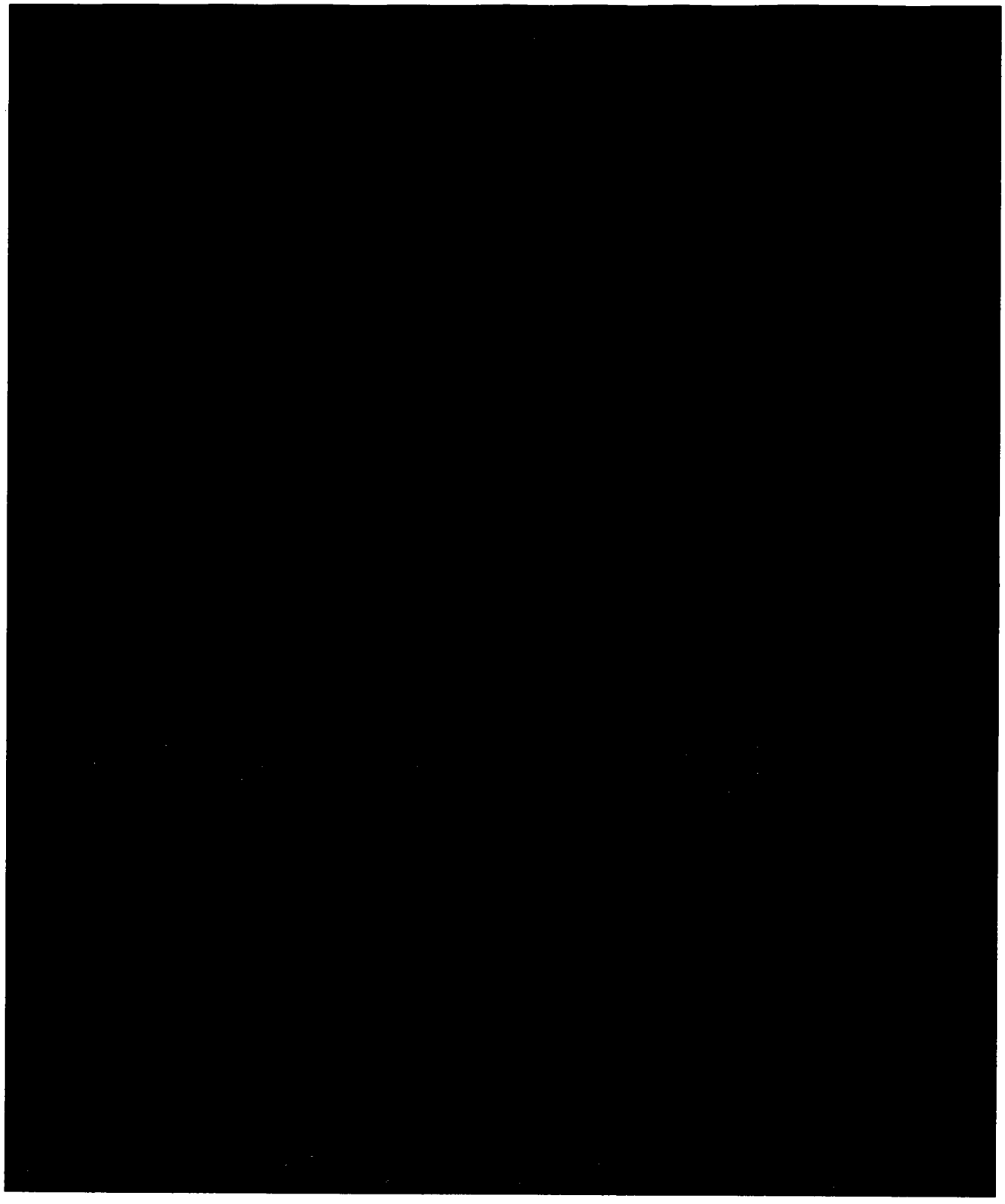
All volunteers fasted for 10 hours prior to and 4 hours after drug administration. No fluids were allowed from 1 hour before dosing until 2 hours after each dose. Fluid was limited to 3000 mL for the period from 2 hours before dosing until 24 hours after dosing. Water was given ad lib after 24 hours of dosing. Standard meal was served after 4 hours of dosing. No caffeine-containing food or beverages were served during the first 24 hours. All subjects were confined from 10 hours pre-dose to 24 hours post-dose. Subjects returned to the clinic for subsequent blood collections.

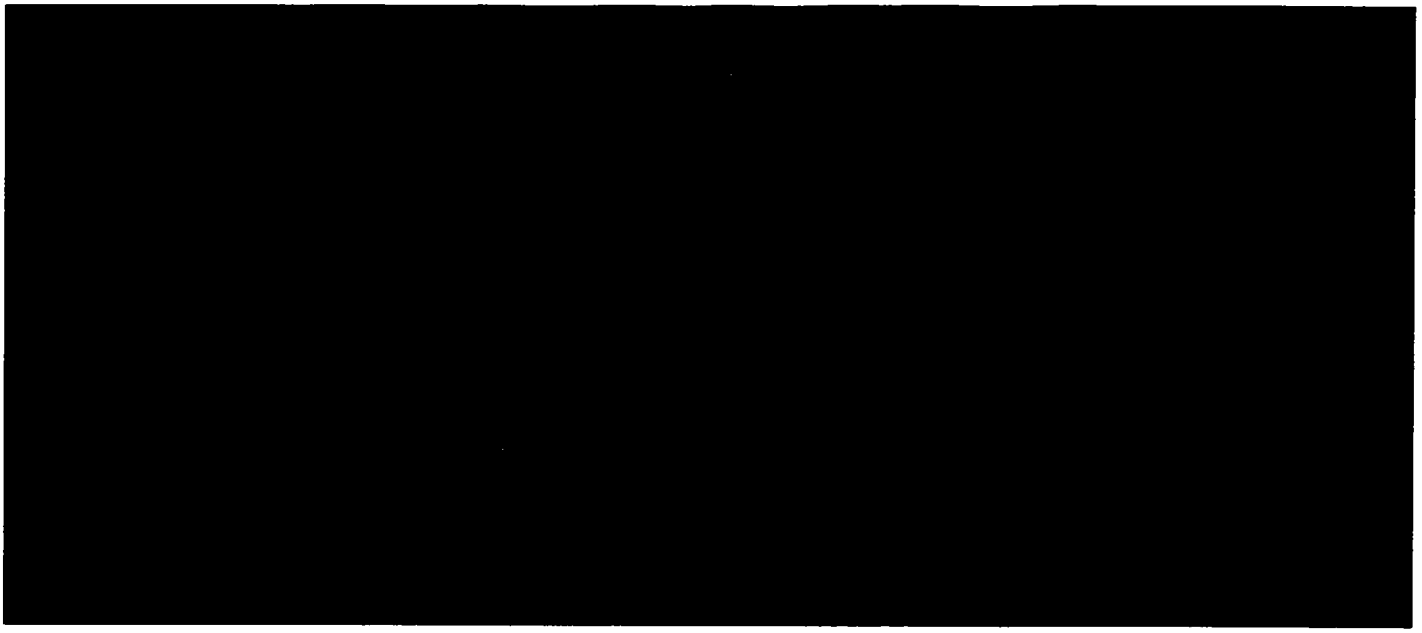
Blood Samples Collection

Seven (7) mL blood samples were collected in vacutainers containing EDTA at 0, .25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 24 hours post-dose and then, at 48hr (Day 3), 72hr (Day 4), 120hr (6 Day), 168hr (Day 8), 240hr (Day 11), 312hr (Day 14), 408hr (Day 18), 480hr (Day 21), 648hr (Day 28), 816hr (Day 35) and 984hr (Day 42). The whole blood samples were kept frozen (-20^0 C) until shipment for analysis.

Assay Methodology







Results:

Fifty (50) volunteers were selected for the study and all fifty (50) volunteers completed the study according to the protocol #B-02024. There were no significant deviations. One subject (#33) was unavailable for his final blood draw (984 hour) as he was transferred to a new job in other state. The only other protocol deviations were the late blood draws upon subject return following release from the clinic (list attached). During clinical evaluations, some adverse events experienced by some subjects were observed. But none of the adverse events were considered serious (List attached). All fifty (50) volunteers' whole blood samples were analyzed. Mean blood methazolamide levels and the pharmacokinetic parameters derived from fifty (50) subjects are presented in Table 1 and Table 2, respectively, below:

Table 1

Mean Blood Methazolamide Levels (μg/mL)

Time (hour) Diff	Test (A) 1 X 50mg Tablet (AAI) Lot # 94106B (Subj=25)	Reference (B) 1 X 50mg Tablet (Lederle) Lot # 370-436 (Subj=25)	A vs B
0	0	0	-
0.25	0.99 (185*)	0.14 (350)	S
0.50	3.43 (77)	1.18 (142)	S
0.75	5.18 (58)	3.15 (93)	S
1.0	6.17 (49)	4.42 (78)	NS
1.5	7.47 (38)	6.00 (62)	NS
2.0	8.22 (30	6.98 (43)	NS
3.0	8.45 (23)	8.38 (22)	NS
4.0	8.30 (22)	8.63 (18)	NS
6.0	8.30 (18)	8.58 (15)	NS
8.0	8.25 (18)	8.32 (16)	NS
12.0	8.08 (17)	8.31 (15)	NS
24.0	8.00 (17)	8.15 (15)	NS
48.0	7.20 (19)	7.34 (17)	NS
72.0	6.80 (19)	6.78 (15)	NS
120	6.01 (19)	6.15 (15)	NS
168	5.18 (20)	5.29 (19)	NS
240	4.41 (19)	4.35 (21)	NS
312	3.76 (19)	3.72 (22)	NS
408	2.95 (24)	3.05 (24)	NS
480	2.60 (23)	2.70 (23)	NS
648	1.91 (26)	1.92 (25)	NS
816	1.39 (32)	1.43 (28)	NS
984	1.01 (38)	1.05** (32)	NS

* Coefficient of Variation
** Mean for 24 subjects
NS Statistically Nonsignificant
S Statistically significant

Table 2

Mean Pharmacokinetic Parameters for Methazolamide in Blood
(Using Least Squares Means)

Parameters	Test (A) (Subj=25)	Ref. (B) (Subj=25)	100xA/B	90% C.I.
AUC_{0-T} ($\mu g.hr/mL$)	3132.52 (20*)	3171.0 (15)	99	90; 108
AUC_{0-inf} ($\mu g.hr/mL$)	3650.68 (22)	3692.84 (21)	99	88; 109
C_{MAX} ($\mu g/mL$)	9.36 (12)	9.53 (13)	98	92; 104
T_{max} (hour)	2.57 (62)	4.66 (113)		
t1/2 (hour)	335.44 (20)	334.04 (14)		
KE (1/hour)	0.0021 (18)	0.0021 (13)		
$LnAUC_{0-T}$	8.0295	8.0446		**90; 108**
Geometric mean	3070.21	3116.92	98	
$LnAUC_{0-inf}$	8.1775	8.1928		**89; 109**
Geometric mean	3559.94	3614.83	98	
LnC_{MAX}	2.2292	2.2456		**92; 105**
Geometric mean	9.2924	9.4461	98	

* Coefficient of Variation

Both test and reference drugs produced peak concentration between 2 to 8 hours after their administration. The differences between the test and reference products in AUC_{0-T}, AUC_{0-inf} and C_{MAX} were less than 2%. All these differences were statistically nonsignificant. The 90% confidence intervals for $LAUC_{0-T}$, $LAUC_{0-inf}$ and LC_{MAX} of the test product remained within the acceptable range of 80 - 125%.

In-Vitro Dissolution:

The firm has conducted an acceptable dissolution testing on Methazolamide tablets. The dissolution testing data are presented in Table 3 below:

Drug (Generic Name): Methazolamide Tablets Firm: AAI, Inc.

Dose Strength: 50 mg, 25 mg

ANDA # 40-011 Submission Date: November 28, 1994

Table -3 In-Vitro Dissolution Testing

I. Conditions for Dissolution Testing:

USP XXII Basket __ Paddle X RPM 100 No. Units Tested: 12

Medium: Acetate Buffer, pH 4.5 Volume: 900 ml

Reference Drug: (Manuf.) Neptazane® 50 mg Tablet (Lederle)

Assay Methodology: [redacted]

II. Results of In-Vitro Dissolution Testing:

Sampling Times (Min.)	Test Product Lot # 94106 Strength (mg) 50 Mean % Dissolved	Range	(CV)	Reference Product Lot # 370-436 Strength (mg) 50 Mean % Dissolved	Range	(CV)
30	98.4	[redacted]	(0.7)	99.5	[redacted]	(1.3)
45	98.6		(1.1)	99.8		(1.4)
60	99.3		(1.4)	100.4		(1.3)

Sampling Times (Min.)	Test Product Lot # 94105 Strength (mg) 25 Mean % Dissolved	Range	(CV)	Reference Product Lot # 366-323 Strength (mg) 25 Mean % Dissolved	Range	(CV)
30	104.4	[redacted]	(2.4)	100.5	[redacted]	(3.7)
45	104.4		(2.3)	100.7		(3.3)
60	104.5		(2.4)	101.9		(3.5)

Formulations:

The compositions of Methazolamide Tablets, 50 mg (lot #94106) and 25 mg (lot #94105) are presented below:

Ingredients	**Strengths (mg/ tablet)**	
	25 mg	**50 mg**
Methazolamide, USP	25.00	50.00
Lactose Hydrous, NF Croscarmellose Sodium, NF Microcrystalline Cellulose NF Magnesium Stearate, NF FD & BLue No. 2 [redacted]	[redacted]	
Total Tablet Weight	**95.60**	**191.20**

Comments:

1. The in vivo bio-study and in vitro dissolution testing have been conducted using test product of lot #94106B, and lot #94106, respectively. The firm has informed the Agency that these two lots are same.

2. The in vivo bioequivalence study conducted on the test and the reference products is acceptable.

3. The comparative in vitro dissolution testing conducted on 50 mg and 25 mg Methazolamide Tablets is acceptable.

4. The formulations of 25 mg and 50 mg Methazolamide Tablets are shown to be proportional.

5. An inspection of the study facilities and an audit of data have been requested through the Division of Scientific Investigations (HFD-340).

Recommendations:

1. The in vivo bioequivalence study conducted by Applied Analytical Industries, Inc. on its 50 mg Methazolamide Tablets of Lot #94106, versus the reference product, Neptazane^{R} 50 mg Tablets manufactured by Lederle has been found acceptable to the Division

of Bioequivalence. The study demonstrates that the test product, Methazolamide 50 mg tablet is bioequivalent to the reference product, Neptazane[R], 50 mg tablet manufactured by Lederle.

2. The in vitro dissolution testing conducted by Applied Analytical Industries, Inc. on its Methazolamide 50 mg Tablet (lot #94106) and 25 mg Tablet (lot #94105) is acceptable. The formulation for the 25 mg strength is proportionally similar to the 50 mg strength of the test product which underwent bioequivalency testing. The waiver of in vivo bioequivalence study requirements for the 25 mg tablet of the test product is granted. The 25 mg tablet of the test product is therefore deemed bioequivalent to the 25 mg tablets of Neptazane[R] manufactured by Lederle.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of acetate buffer, pH 4.5 at 37^0 C using USP XXIII apparatus II (paddle) at 100 rpm. The test drug should meet the following specifications:

   Not less than [redacted] of the labeled amount of the drug in the dosage form is dissolved in 45 minutes.

[redacted]
Sikta Pradhan, Ph.D.
Division of Bioequivalence
Review Branch I

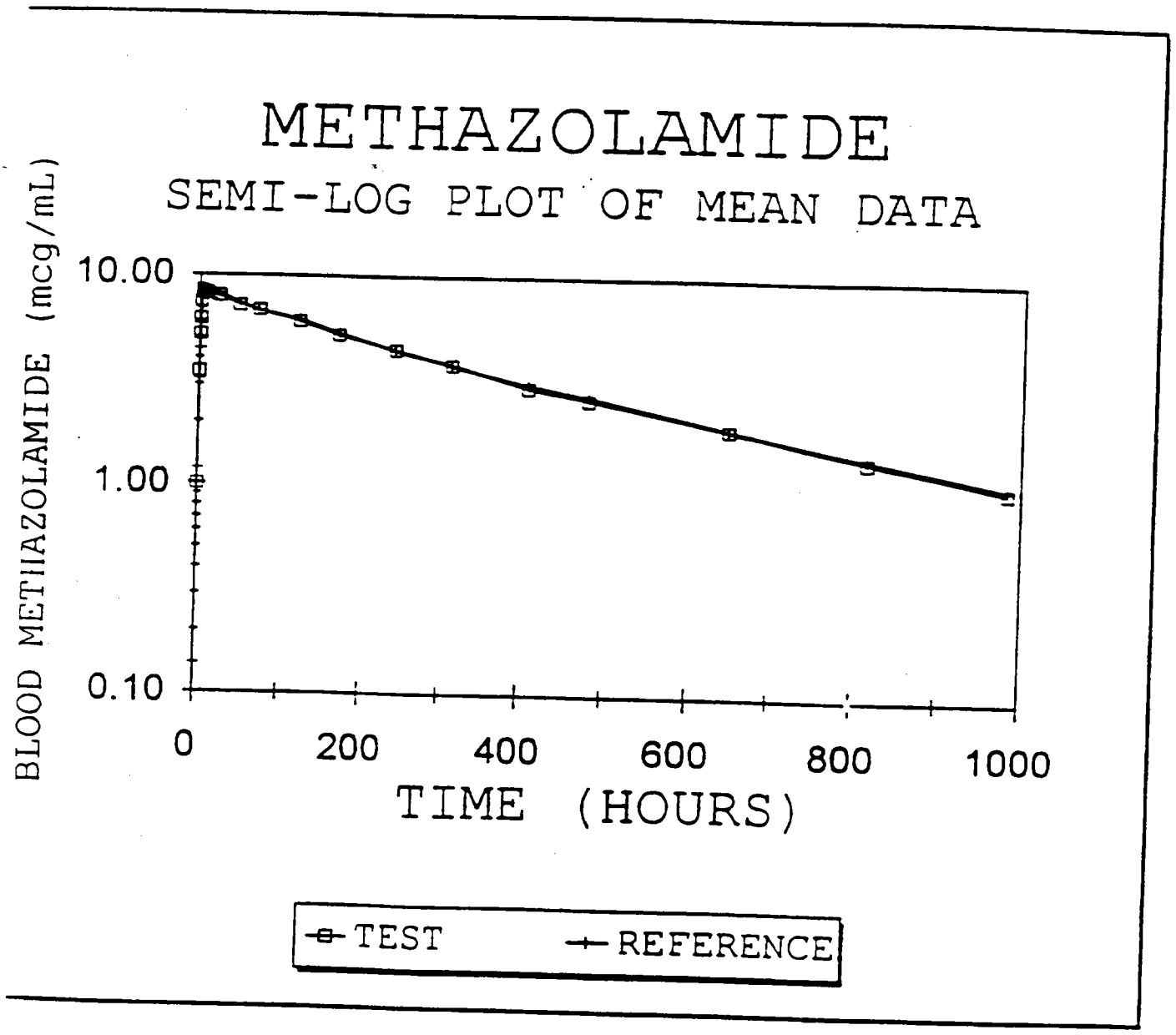
RD INITIALED YCHUANG
FT INITIALED YCHUANG -- [redacted] 8/11/95

[redacted]

Concur: -- [redacted] Date: 8/17/95
Keith K. Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA # 40-011 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-652 (Huang, Pradhan), Drug File, Division File.

SP/07-18-95/X:\wpfile\Pradhan\40011SDW.N94


METHAZOLAMIDE
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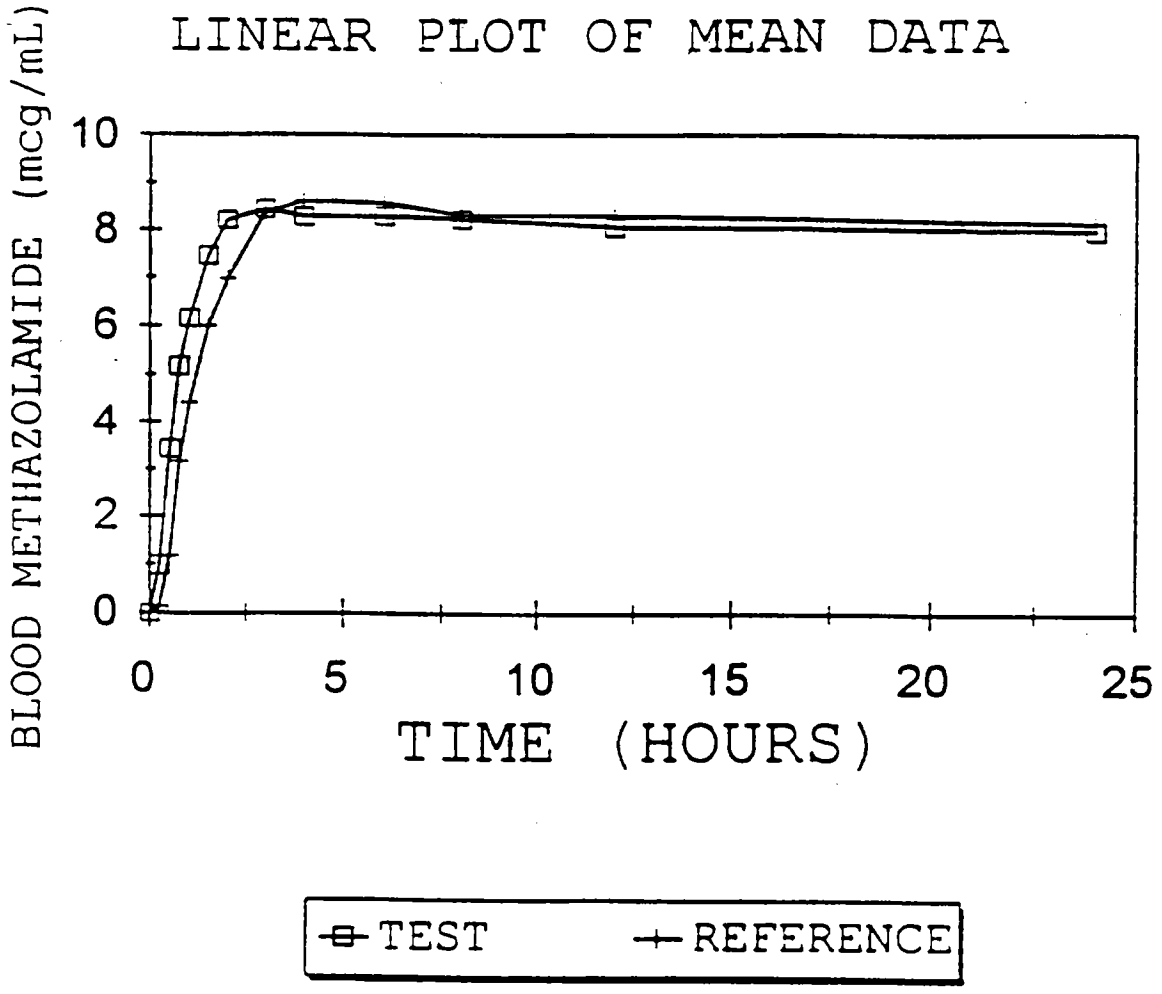
BLOOD METHAZOLAMIDE (mcg/mL)
10.00
1.00
0.10
0
200
400
600
800
1000
TIME (HOURS)
TEST
REFERENCE

METHAZOLAMIDE

LINEAR PLOT OF MEAN DATA



Adverse Experiences

During this clinical evaluation, the following adverse events were observed by the staff, or reported by the volunteers.

Subject	Assigned Drug*	Adverse Event	Severity	Date of Onset	Hours Post-Dose	Time (Hrs) Duration	Comments
16. [redacted]	T	Headache	Moderate	06/25/94	7	3.25	No therapy required. Resolved spontaneously. Possibly drug related.
		Headache	Severe	06/25/94	14	10	Subject put in supine position. Cold cloth applied to forehead. Resolved spontaneously. Possibly drug related.
		Headache	Mild	06/26/94	23.5	4	No therapy required. Resolved spontaneously. Possibly drug related.
		Diarrhea	Severe	06/27/94	48	24.5	No therapy required. Resolved spontaneously. Unlikely drug related.
31 [redacted]	R	Headache	Mild	06/25/94	7.5	3	No therapy required. Resolved spontaneously. Possibly drug related.
		Headache	Moderate	06/25/94	10.5	13	No therapy required. Resolved spontaneously. Possibly drug related.
		Headache	Moderate	06/26/94	28.5	6	No therapy required. Resolved spontaneously. Possibly drug related.
		Headache	Moderate	06/27/94	46.5	12	No therapy required. Resolved spontaneously. Possibly drug related.
36. [redacted]	T	Headache	Moderate	06/25/94	5.5	2	No therapy required. Resolved spontaneously. Possibly drug related.

*T = Test product
R = Reference product

Appendix VIII

A Relative Bioavailability
Parallel Study of Methazolamide
(50 mg) Tablets
Early/Late Blood Draw Times

Subject	Day	Hour	# Hours/Minutes Early/Late	Comment
0[redacted]	21	480	40 min. late	Overslept
0[redacted]	21	480	8 hrs. 30 min. late	Work
0[redacted]	28	648	8 hrs. 31 min. late	Work
0[redacted]	35	816	6 hrs. 59 min. late	Work
0[redacted]	42	984	4 hrs. 39 min. late	Work
0[redacted]	4	72	34 min. early	Work
0[redacted]	6	120	34 min. early	Work
0[redacted]	14	312	34 min. early	Work
0[redacted]	18	408	34 min. early	Work
0[redacted]	21	480	30 min. early	Work
08[redacted]	42	984	12 hrs. early	Work
11[redacted]	6	120	4 min. late	Traffic
11[redacted]	11	240	32 hrs. 24 min. late	Accident
11[redacted]	14	312	3 hrs. 54 min. late	Forgot
12[redacted]	14	312	42 min. late	Overslept
16[redacted]	8	168	16 hrs. 28 min. early	Going out of town
19[redacted]	18	408	40 min. early	Work
19[redacted]	21	480	6 hrs. 50 min. late	Forgot
20[redacted]	18	408	35 min. late	Overslept
21[redacted]	4	72	54 min. late	Overslept
21[redacted]	6	120	3 hrs. 4 min. late	Overslept/forgot
21[redacted]	8	168	3 hrs. 13 min. late	Overslept
21[redacted]	11	240	62 min. late	Overslept
21[redacted]	14	312	40 min. late	Overslept
21[redacted]	18	408	35 min. late	Overslept
21[redacted]	21	480	3 min. late	Overslept
21[redacted]	28	648	7 hrs. 2 min. late	Overslept
21[redacted]	35	816	6 hrs. 54 min. late	Overslept
21[redacted]	42	984	7 hrs. 54 min. late	Overslept
22[redacted]	28	648	1 hr. 29 min. late	Car trouble
23[redacted]	8	168	14 hrs. 42 min.early	Going out of town
23[redacted]	18	408	49 min. late	Overslept

Appendix VIII

A Relative Bioavailability
Parallel Study of Methazolamide
(50 mg) Tablets
Early/Late Blood Draw Times

Subject	Day	Hour	# Hours/Minutes Early/Late	Comment
2[redacted]	8	168	1 hr. 47 min. late	Overslept
2[redacted]	4	72	10 min. early	Work
2[redacted]	18	408	16 min. early	Work
2[redacted]	21	480	20 min. early	Work
2[redacted]	8	168	58 min. late	Overslept
2[redacted]	42	984	14 hrs. 26 min. early	Going out of town
2[redacted]	11	240	5 hrs. 40 min. late	Car trouble
2[redacted]	35	816	60 min. late	Overslept
3[redacted]	14	312	47 min. late	Worked late
3[redacted]	21	480	64 min. late	Worked late
3[redacted]	28	648	50 min. late	Worked late
3[redacted]	35	816	61 min. late	Worked late
3[redacted]	4	72	64 min. late	Overslept
3[redacted]	8	168	27 min. late	Overslept
3[redacted]	11	240	45 min. late	Overslept
3[redacted]	28	648	15 min. late	Overslept
3[redacted]	42	984	No SAMPLE	New job in Texas
34[redacted]	8	168	16 min. late	Overslept
34[redacted]	21	480	13 min. late	Overslept
34[redacted]	35	816	14 hrs. 43 min late	Out of town
35[redacted]	4	72	30 min. early	Work
35[redacted]	6	120	33 min. early	Work
35[redacted]	8	168	31 min. early	Work
35[redacted]	11	240	33 min. early	Work
35[redacted]	14	312	31 min. early	Work
35[redacted]	21	480	33 min. early	Work
36[redacted]	42	984	6 hrs. late	Car trouble
37[redacted]	35	816	40 min. late	Overslept
44[redacted]	21	480	19 min. late	Overslept
45[redacted]	14	312	22 min. late	Overslept
47[redacted]	8	168	7 min. late	Overslept
48[redacted]	14	312	22 min. late	Overslept

Appendix VIII

A Relative Bioavailability
Parallel Study of Methazolamide
(50 mg) Tablets
Early/Late Blood Draw Times

Subject	Day	Hour	# Hours/Minutes Early/Late	Comment
48. [redacted]	35	816	35 min. late	Overslept
49. [redacted]	4	72	20 min. late	Overslept
49. [redacted]	8	168	15 hrs. 10 min. early	Going out of town
50. [redacted]	14	312	22 min. late	Overslept

SUBJECT CHARACTERISTICS

AAI/Study No. B-02024 - Methazolamide 50 mg Tablets

Sub No.	Sub. I.D.	Age (Years)	Height (Inches)	Weight (Pounds)	Frame	Allowable Weight Range*
1	[redacted]	27	69	168	Medium	133 - 176
2		31	69	182	Large	140 - 194
3		30	74	210	Large	155 - 215
4		35	72	173	Medium	141 - 187
5		37	67	148	Medium	128 - 169
6		34	69	174	Large	140 - 194
7		18 ✓	69	159	Medium	133 - 176
8		21	71	200	Large	145 - 202
9		40	75	175	Medium	150 - 200
10		33	71	185	Large	145 - 202
11		29	73	178	Large	151 - 211
12		21	72	165	Medium	141 - 187
13		32	70	185	Large	142 - 198
14		36	76	212	Large	163 - 228
15		44 ✓	67	181	Large	134 - 182
16		23	67	170	Large	134 - 182
17		27	64	145	Medium	123 - 159
18		39	67	180	Large	134 - 182
19		24	71	192	Large	145 - 202
20		18	71	143	Medium	139 - 183
21		20	72	190	Large	148 - 207
22		24	73	210	Large	151 - 211
23		23	68	149	Medium	131 - 173
24		26	67	171	Large	134 - 182
25		21	71	183	Large	145 - 202
26		33	67	160	Medium	128 - 169
27		42	73	208	Large	151 - 211
28		22	70	176	Medium	136 - 179
29		20	69	153	Medium	133 - 176
30		31	68	167	Medium	131 - 173
31		43	75	214	Large	159 - 222
32		35	70	193	Large	142 - 198
33		39	69	190	Large	140 - 194
34		20	67	162	Medium	128 - 169
35		25	67	141	Small	124 - 159
36		18 ✓	71	161	Medium	139 - 183
37		18	73	204	Large	151 - 211
38		19	68	155	Medium	131 - 173
39		21	70	151	Medium	136 - 179
40		28	68	185	Large	137 - 187
41		44 ✓	68	144	Medium	131 - 173
42		20	72	173	Medium	141 - 187
43		28	63	138	Medium	120 - 157
44		39	73	184	Large	151 - 211
45		18	69	140	Medium	133 - 176
46		32	70	185	Large	142 - 198
47		31	71	194	Large	145 - 202
48		20	69	140	Small	128 - 166
49		20	71	144	Medium	139 - 183
50		19	72	147	Medium	141 - 187
	Means	28	70	172.9		

*Ranges are ± 10% of ideal body weight range based on height and frame size; see Appendix A of Protocol B-02024.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA/~~AADA~~ # 40-011 SPONSOR: HAI, Inc.
DRUG: Methazolamide
DOSAGE FORM: Tablets
STRENGTH(s): 25 mg & 50 mg
TYPE OF STUDY: Single/~~Multiple~~ Fasting/~~Fed~~ (or ~~Equiv~~)
STUDY SITE: [redacted]

STUDY SUMMARY: A randomized, one-period, parallel design study in 50 subjects using 50mg Tablets (HAI) vs. 50 mg Neptazane® of Lederle & 90% C.I.

DISSOLUTION: Test product met USP XXIII dissolution specs of Q = [redacted] in 45 min.

PRIMARY REVIEWER: BRANCH:
INITIAL: [redacted] DATE: 8/16/95

BRANCH CHIEF: BRANCH:
INITIAL: [redacted] DATE: 8/16/95

DIRECTOR
DIVISION OF BIOEQUIVALENCE
INITIAL: [redacted] DATE: 8/28/95

DIRECTOR
OFFICE OF GENERIC DRUGS
INITIAL: DATE: